MIPLC Studies 6

Martina Schuster

Patenting Proteomics

Patentability and Scope of Protection of Three-Dimensional Protein Structure Claims under German, European and US Law

Nomos

MIPLC Munich Intellectual Property Law Center
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Gedruckt mit Unterstützung des Förderungs- und Beihilfefonds Wissenschaft VG Wort

Printed with support by "Förderungs- und Beihilfefonds Wissenschaft VG Wort".

Die Deutsche Nationalbibliothek verzeichnet diese Publikation in der Deutschen Nationalbibliografie; detaillierte bibliografische Daten sind im Internet über http://dnb.d-nb.de abrufbar.

The Deutsche Nationalbibliothek lists this publication in the Deutsche Nationalbibliografie; detailed bibliographic data is available in the Internet at http://dnb.d-nb.de .

Zugl.: München, Univ., Diss., 2009

ISBN 978-3-8329-4748-4

1. Auflage 2010

Acknowledgements

This dissertation was accepted by the Ludwig-Maximilians-University Munich for the degree of doctor juris in March of 2009. It takes into account the law until the end of 2008.

The thesis would not have been written without the help and support of many different people from diverse backgrounds. The most sincere appreciation goes to my advisor Prof. Dr. Dres. h.c. Joseph Straus for his continuing help and encouragements, and to Prof. Dr. Michael Lehmann for his efforts as second referee.

I am also very grateful to the Honorable Judge Randall R. Rader for his advice and the deep insights into U.S. and comparative patent law during my time as a Visiting Scholar at the Federal Circuit Court in Washington, DC. Many thanks also to Professor Robert Brauneis and his wife for helping me and my family to settle in in Washington, DC, to Professor John Duffy for organizing access to the Jacob Burns Law Library, to Chris Holman, associate professor at the University of Missouri-Kansas City School of Law, for creating his most useful IP and biotech listserv for academics "IpBiotechProfs" and his invitation to join it, and to Josh Sarnoff, Assistant Director of the Glushko-Samuelson Intellectual Property Law Clinic in Washington DC, for reading the U.S. Patent Law chapter and sending me several pages with comments.

While working on the thesis, I benefited a lot from conversations with my colleagues at the Max-Planck-Institute for Intellectual Property, Competition and Tax Law in Munich, in particular Marc-Oliver Mackenrodt, Peter Ganea and Wolrad Prinz zu Waldeck und Pyrmont. Furthermore, Clara Sattler provided most valuable comments on the scientific background chapter.

Many thanks also to Christian Kummer SJ, professor of natural philosophy at the Munich School of Philosophy for letting me participate in his bioethical colloquium.

Many thanks also to my family and friends: my parents for their never ending support and patience; Tim and Niels Schuster, as well as Dorothee Gottwald for their huge efforts with reading corrections in exemplary ways; Marianne Menth for her substantive scientific direction.

Never enough thanks to my husband Uli for his encouragement, academic spirit and just being. He always got my back through thick and thin.

I dedicate this thesis to my son Samuel, the bringer of joy and light. May he always think of proteins as the central building blocks for all life on earth.

November 2009 *Martina Schuster*

Contents

List of Abbreviations

1-D	1-dimensional
2-D	2-dimensional
3-D	3-dimensional
ABS	Antilock Brake Systems
ACTH	Adrenocorticotrophic hormone
AG	Aktiengesellschaft
AIPLA	American Intellectual Property Law Association
AIPPI Journal	Journal of the International Association for the Protection of Intellectual Property
Annu Rev Phys Chem	Annual review of physical chemistry
ARC	Act against Restraints of Competition
Art.	Art.
ATCC	American Type Culture Collection
Aufl.	Auflage
Bd. Pat. App. & Int.	Board of Patent Appeals and Interferences of the United States Patent and Trademark Office
beta-IFN	beta-Interferon
BGB	Bürgerliches Gesetzbuch
BGBL.	Bundesgesetzblatt
BGH	Bundesgerichtshof, Federal Supreme Court
BGHZ	Bundesgerichtshof, Zivilsachen
BIPMZ	Blatt für Patent-, Muster-, und Zeichenwesen
BMJ	German Ministry of Justice
BSE	bovine spongiform encephalopathy
CAFC	Court of Appeals for the Federal Circuit
Cal.	California
C.C.P.A .	Court of Customs and Patent Appeals
C.C.D. Mass.	United States District Court for the District of Massachusetts
cDNA	complementary DNA
cert. denied by	Certiorari Denied by
CFR	Code of Federal Regulations
Cir.	Circuit
CJD	Creutzfeld-Jakob disease
Co.	Company
Corp.	Corporation
COX-1	Cyclooxygenase-1
COX-2	Cyclooxygenase-2

CR	Computer und Recht
DNA	Deoxyribonucleic acid
DOE	U.S. Department of Energy
EBA	Enlarged Board of Appeal
EBI	European Bioinformatics Institute
EC	European Council
ECJ	European Court of Justice
ed.	Edition
E. coli	Escherichia coli
e.g.	for instance (exempli gratia)
EMBL	European Molecular Biology Laboratory
EPA	Europäisches Patentamt
EPC	European Patent Convention
EPO	European Patent Office
Epo	Erythropoietin
EPÜ	Europäisches Patentübereinkommen
EST	Expressed Sequence Tag
et al.	et alii/et alia
etc.	et cetera
EU	European Union
EU-RL	EU-Richtlinie
e.V.	eingetragener Verein
FAZ	Frankfurter Allgemeine Zeitung
FDA	U.S. Food and Drug Administration
FDCA	Federal Food, Drug and Cosmetic Act
Fed. Cas.	Federal Cases
Fed. Cir.	Federal Circuit
Fed. Reg.	Federal Register
FFII	Foundation for a Free Information Infrastructure
Fig.	Figure
FN	Footnote
FT/MS	Fourier transformation mass spectrometry
ftp	File Transfer Protocol
GA-EPO	EPO product made using a process called ‘gene activation’
GG	Grundgtesetz
GmbH	Gesellschaft mit beschränkter Haftung
GPA	German Patent Act
GRUR	Gewerblicher Rechtsschutz und Urheberrecht
GRURInt.	Gewerblicher Rechtsschutz und Urheberrecht, Internationaler Teil
HPI	Human Proteomic Initiative

HPRD	Human Protein Reference Database
HTS	*idem*
IIC	International Review of Industrial Property and Copyright Law
Inc.	Incorporated
IND	Investigational New Drug
Indus.	Industry
IP	Intellectual Property
IU	International unit
J.	Journal
J. Biol. Chem.	Journal of Biological Chemistry
Jan.	January
JIBL	Journal of International Biotechnology Law
JP	Japan
JPO	Japanese Patent Office
J Struct Biol	Journal of Structural Biology
J Struct Funct Genomics	Journal of Structural and Functional Genomics
K_M	Michaelis-Menten constant
L.J.	Law Journal
Ltd.	Limited
MALDI-TOF	matrix assisted laser desorption time of flight
MittdtschPatAnw	Mitteilungen der deutschen Patentanwälte
Mmole	Millimolar
mRNA	messenger ribonucleic acid
NAPS	Nonassociated polymeric structures
NBRF	National Biomedical Research Foundation
NASA	National Aeronautics and Space Administration
NCBI	National Center for Biotechnology Information
NDA	New Drug Application
N.D. Cal.	United States District Court, Northern District of California
NESP	Novel Erythropoiesis Stimulating Protein
NHLBI	National Heart, Lung, and Blood Institute
NIH	National Institutes of Health
NINDS	National Institute of Neurological Disorders and Stroke
NJW	Neue Juristische Wochenschrift
No.	Number
Nov.	November
NMR	Nuclear Magnetic Resonance
N. Publ.	Not Published
OJ	Official Journal
ORF	Open reading frame

par(a)	paragraph
Pat.	Patent
PatG	Patentgesetz
PC	Paris Convention
PCT	Patent Cooperation Treaty
PDB	Protein Data Bank
PIR	Protein Information Resource
PNAS	Proceeding of the National Academy of Science
Prog Biophys Mol Biol	Progress in Biophysics & Molecular Biology
Proc Natl Acad Sci USA	Proceeding of the National Academy of Science of theUnited States of America
PrP	Prion Protein
PrP-C	cellularPrP
PrP-Sc	PrPscrapie
PSD	Protein Sequence Database
PTM	Posttranslational modifications
PTO	Patent and Trademark Office
P.T.O.	U.S. Patent and Trademark Office
Bd.Pat.App. & Int.	Board of Patent Appeals and Interferences
Q.J.	Quarterly Journal
R&D	Research and Development
RCSB	Research Collaboratory for Structural Bioinformatics
RG	Reichsgericht
RGZ	Reichsgericht Zivilsachen
Rn.	Randnummer
RNA	Ribonucleic acidr
RNAS	ribosomal RNAS
R.P.C.	Reversed-phase chromatography
RPC	Reports of Patents, Design and Trade Mark Cases
RPTK	Receptor protein tyrosine kinase
RUCTLJ	Rutgers computer and technology law journal
Sec.	Section
SEQ ID NO	Sequence Identification Number
SIB	Swiss Institute of Bioinformatics
SNPS	Single Nucleotide Polymorphisms
Suppl.	Supplement
Sum. of Facts and Sub.	Summary of Facts and Submissions
SWISS-Prot	Annotated protein sequence databank
TAZ	Tageszeitung
TBA	Technical Board of Appeals

t-PA	tissue plasminogen activator protein
Tech.	Technology
TNK	bioengineered variant of t-PA
TrEMBL	Computer-annotated supplement to Swiss-Prot
TRIPS	Agreement on Trade Related Aspects of Intellectual Property Rights
uEpo	Urine purified erythropoietin
U.Chi.L.Rev.	University of Chicago Law Review
UniProt	Universal Protein Resource
U.S.C.	United States Code
USCA	United States Court of Appeal
USPQ	United States Patent Quarterly
USPTO	United States Patent and Trademark Office
V	(Enzyme-)Velocity
V_{max}	maximum velocity of the enzyme
v.	von, vom bzw. versus
vs.	versus
Vol.	Volume

Chapter 1: Introduction

The Human Genome Project revealed that the human organism contains far fewer genes than proteins. The fact that approximately 33,000 genes encode more than 200,000 proteins invalidated the long-held assumption that one gene encodes a single protein.[1] In addition, the discrepancy between the number of genes and the number of proteins refocused attention on the latter.[2] The pharmaceutical and economic interest in protein analysis was further stimulated when studies demonstrated that even small structural variations – such as posttranslational or interactive modifications – could have an enormous impact on the physiology of the entire cell.[3]

The importance of these modifications can be illustrated using as an example the family of brain diseases known as "transmissible spongiform encephalopathies", or TSEs.[4] Among these, the Creutzfeld-Jakob Disease (CJD) and the Bovine Spongiform Encephalopathies (BSE) have alarmed scientists, politicians and the public worldwide, after an unusually large number of cases arose in Great Britain. CJD and its most important variant, vCJD, lead to strong personality changes, problems with balance and coordination and finally coma and death, just months after patients have developed the first symptoms. Until the early 1980s, there was no clear understanding of the causes of the disease. Consequently, medical treatments could not be developed. Most scientists conjectured that a virus was the most probable cause of the infection. This changed when Stanley Prusiner, a researcher at the University of California at San Francisco, suggested that JCD was not caused by a known pathogen, but by a protein characterized by a peculiar three-dimensional structure. While the hypothesis was harshly criticized initially, the idea that misfolded proteins

1 The number of different protein molecules expressed by the human genome is probably closer to a million than to the 200,000 generally estimated by genome scientists. The actual amount of proteins in the human organism is still unknown, but some researchers believe that there exist as many as two million, see Service, Robert F., Gene and Protein Patents Get Ready to Go Head to Head, 294 Science 2001, 2082, 2082. The number of genes of the human organism is barely higher than the number of genes characterizing the roundworm Caenorhabditis elegans. The fact that the human genome is able to produce such a high degree of complexity with only a few genes is generally attributed to the phenomenon of alternative splicing. Alternative splicing is explained in Pennisi, Elizabeth, Why Do Humans Have So Few Genes?, 309 Science 2005, 80 and Jollès, Pierre/Jörnvall, Hans, Proteomics in Functional Genomics, Protein Structure Analysis, Basel et al. 2002, XI. See also Straus, Joseph, Produktpatente auf DNA-Sequenzen – eine aktuelle Herausforderung des Patentrechts, GRUR 2001, 1016, 1019f.

2 Bohrer, Robert A., Proteomics: The Next Phase in the Biotechnology Revolution and the Next Challenge for Biotechnology Law, 22 Biotechnology Law Report 2003, 263, states that "[t]he massive trove of genetic information has produced more questions than answers".

3 Straus, Joseph, Produktpatente auf DNA-Sequenzen – eine aktuelle Herausforderung des Patentrechts, GRUR 2001, 1016, 1019f.

4 The term TSE is derived from the spongy holes that are present in infected brains.

(called prions, or proteinaceous infectious parts) were responsible for CJD is now widely accepted.[5] Prusiner received the Nobel Prize[6] in 1997, and prions can be considered the first 3-D proteomic structures that penetrated the consciousness of the wider public.[7]

The human genome project and subsequent "post-genomic"[8] studies clearly demonstrated that these 3-D structures are of prime importance.[9] More importantly, they revealed that molecular biology could only be understood as a dynamic system, which uses a wide range of regulatory mechanisms to control its activities.[10] The dynamic changes in proteins, such as their seemingly endless modifications and interactions, their binding activity or self-regulatory adjustments, can be considered their crucial element. This acknowledgement was the starting point for the so-called "post-genomic" era, where proteomics – the science of the proteome as defined below – begins.[11]

5 See Prusiner, Stanley B./Scott, Michael R., Genetics of Prions, 31 Annual Revue of Genetics 1997, 139. A major advancement in the study of prions and prion-based diseases was the discovery and purification of a protein characterized as prion protein ("PrP"). A leading theory is that prion diseases are caused by the modification of PrP from PrP.sup.C into PrP.sup.Sc. The precise biological function of PrP.sup.C is still unknown.

6 Prusiner, Stanley B., Nobel Lecture, 95 PNAS 1998, 13363.

7 Neurodegenerative diseases like Alzheimer's provide another example of the importance of protein folding, with even larger social and economic implications, see Whitford, David, Proteins: Structure and Function, Hoboken, NJ 2005, 468-470.

8 The term "post-genomic" refers to research techniques that became relevant after the disclosure of genetic sequences; see Barton, John H., United States Law of Genomic and Post-Genomic Patents, 33 IIC 779, 786 (2002).

9 Thus, life science research moved from a genome-based level that emphasized the study of the gene to a 'post-genomic' level focusing on information regarding proteins; Masuoka, Kunihisa, Study on the Ways of Protection of Post-Genome Research Products, IIP Bulletin 2002, 84-95, 84. Many scientist hold the view that proteomics involves complexities that scholars of genomics do not encounter. "If genomics resembles the Matterhorn, proteomics is like the Mount Everest", see Gwynne, Peter/Heebner, Gary, Drug Discovery and Biotechnology Trends – Proteomics I: In Pursuit of Proteins, Science 2003, 665, 665.

10 Straus, Joseph, Produktpatente auf DNA-Sequenzen – eine aktuelle Herausforderung des Patentrechts, GRUR 2001, 1016, 1019f. The disclosure of the human genome also showed that systems of DNA regulation have a much stronger impact than expected.

11 Barton, John H., United States Law of Genomic and Post-Genomic Patens, 33 IIC 779 (2002); Peltonen, Leena/McKusick, Victor A., Dissecting Human Disease in the Postgenomic Era, 291 Science 2001, 1224. In many cases, a better picture of the molecular biology of a cell is only achieved by the study of proteins, as emphasized in Russell, Robert B., Genomics, Proteomics and Bioinformatics: All in the Same Boat, 3 Genome Biology 2002, REPORTS 4034. Nevertheless, the Human Genome Project provides powerful insights into human diseases. It thus has been "worth the effort", as stated by Daiger, Stephen P., Was the Human Genome Project Worth the Effort? 308 Science 2005, 362, 364. The new proteomic view of a dynamic molecular biology inspired the further development of "genomic tools", such as 'Genome Fingerprint Scanning', which is usually combined with the proteomics technology of mass spectrometry, see Sender, Aaron J., Decoding Recorders for Protein ID, Genome Technology 2003, 26, 27.

One of the key promises of proteomics is that of drug design, because most drugs act through the modification of a specific protein. Proteomic technologies may speed up the screening of new pharmaceutical compounds and thus lower time and money consuming investments.[12] If a pharmaceutical company is able to market a drug only one year earlier, this could amount to $500 million additional profits.[13] Another promising and accelerating field is biomarker development. The term 'biomarker' refers to biochemical molecules that are used to measure the progression of disease or the effects of pharmaceutical treatment. Biomarkers are increasingly important in the progress of drug design, because they provide novel and specific means for early detection and diagnosis of diseases such as cancer, HIV or hepatitis.[14]

The era of proteomics thus offers a wide range of opportunities and challenges for research and development. At the same time, however, it creates new challenges for the individuals and institutions constituting the biotechnological research complex, including patent law as its central legal institution. Here, the main question is whether and how traditional standards must be readjusted in order to cope with the nature of this dynamic scenario envisioned by many. To answer this question, however, it is of paramount importance to answer yet another question: How do patent law institutions, in particular patent offices, currently treat proteomic inventions, and how would they treat the range of inventions that can be expected to materialize in the not so distant future? Due to the novelty and broad scope of the subject, a systematic description of current practices is still lacking, and the analysis below attempts to provide first steps towards a comprehensive summary of existing practices.

More generally, this study provides a comparative analysis of patentability issues related to proteomics inventions with the following two main objectives: to clarify current views and practices and to derive legal policy conclusions related to proteomic patents. It aims at identifying the issues that the major players in the field (research units, companies, lawyers, patent offices, courts and legislature) will be con-

12 The scientific community frequently emphasizes that the efficiency of drug design is significantly enhanced by proteomics. It is held that genomic information had little effect on drug discovery. In the long run, however, the advanced understanding of the roles genes and proteins play in the organism does promise new approaches to the comprehension of diseases; Hall, Stephan S., Revitalizing drug discovery, Technology Review October 2003, 39, 39

13 Vorndran, Charles/Florence, Robert L., Bioinformatics: Patenting the Bridge between Information Technology and the Life Science, 93 IDEA – The Journal of Law and Technology 2003, 93, 104. Bioinformatics may also speed up discovery by screening precise drug targets at an early stage. See also Howard, Ken, The Bioinformatics Gold Rush, Scientific Am. 58, 58 (July 2000).

14 Kleist, Peter, Biomarker und Surrogat-Endpunkte: Garanten für eine schnellere Zulassung von neuen Arzneimitteln? 83 Schweizerische Ärztezeitung 2002, 2347, 2347; as for recent discoveries in the field of biomarkers, see Zucht, Hans-Dieter, Biomarker Discovery, Transkript 2004, 48; Deutsche Gesellschaft für Proteomforschung, Biomarker Discovery and Imaging Proteomics,Transkript 2004, 57; the search for disease biomarkers using proteomics is also referred to as "disease proteomics"; Hanash, Sam, Disease proteomics, 422 Nature 2003, 226, 229.

fronted with in the years to come. By discussing alternative approaches to deal with these problems, the study also contributes to the further development of legal standards. In the course of this analysis, it will become clear that proteomics touches yet another important policy issue. When the first DNA patents were granted, many observers expressed the concern that they would constitute the basis for permanent and harmful monopoly positions, with adverse effects on price setting behavior and research dynamics. In particular, it was hypothesized that gene patents would provide disincentives to invest in research and development activities that would lead to the pharmaceutical innovations originally envisioned. As will become clear below, proteomics is an important test field in this regard. It can provide some first indications as to whether the original fears were legitimate.

To summarize, the proteomic era confronts legal experts with a set of important and exciting questions. To answer these questions, chapter II introduces the reader to the scientific background of proteomics. This includes a discussion of different protein structural folding levels. Moreover, the relative importance of primary, secondary and tertiary protein structure is discussed with regard to biological functions, demonstrating why the tertiary stage is typically the major focus of pharmaceutical research. Furthermore, an overview of basic proteomic analysis techniques, as well as an illustration of major proteomic organizations and networks, will be provided. Chapter III looks at the patentability of proteomic inventions, and starts with an overview of general patentability requirements in both the European and the U.S. patent law system. The statutory background and the decisive case law are presented, with the focus set on applications related to proteomics. In a next step, the second part of Chapter III will go through a case study that illustrates how claims directed to typical proteomic features such as complex protein structures or bioinformatics research tools are likely going to be approached from the legal point of view. Among other things, the discussion will emphasize differences in the legal criteria and practices being applied in the U.S. and Europe in the course of the examination process.

The remainder of the study is devoted to the question of adequate scope of protection for proteomic inventions (chapter IV). Chapter IV first discusses claim construction issues related to the scope of protection. With patent infringement being treated under German law, particularly the German perspective will be taken into account. In a second step, a concrete claim analysis under both German and U.S. law will be carried out. Using a broad spectrum of claims from the field of 3-D protein structure, the scope of protection of DNA and protein patents is analyzed. Chapter V summarizes the major findings of the study regarding patentability and scope of protection and derives a set of core conclusions with respect to the broader policy implications of these findings.

Chapter 2: Scientific background

In order to understand the legal treatment of 3-D protein structure-related claims, a thorough understanding of basic proteomic concepts is necessary. This chapter therefore provides a brief introduction into the scientific background of the subject. Since proteomics is a rapidly growing and dynamically changing field, it is of course unrealistic to provide a complete and exhaustive treatment. Instead, the focus will be on issues that are indispensable as a background and relevant from the point of view of intellectual property rights.

After defining the term "proteomics", the role of proteins in biological organisms will be reviewed, with special emphasis on theories of amino acid structure and protein folding. Since many pharmaceutical applications of proteomics deal with specific folding details, the concepts of "structurally similar, sequence dissimilar proteins" as well as the basic idea of "posttranslational modifications" have to be introduced. In section C, the role played by genetic information in the shaping of proteomic structures will be assessed. This subject is of prime importance for two reasons. First, from a biological point of view, recent proteomic research has significantly changed the conceptual treatment of protein encoding. In particular, the close association of genetic code and protein functionality has become increasingly blurred. Second (and closely related), this may have important implications for the legal treatment of proteomics, since questions of patent dependency have to be evaluated in light of the relative importance of genetic information. The chapter closes with a description of the most important proteomic research techniques. The diversity of active research areas shows how dynamic the field of proteomics is, and provides a sense of the types of issues confronting the patent system.

A. Definition of the Term

"Proteomics" is derived from the term "proteome", which was first used in 1994 during a scientific conference in Siena, Italy. At that time, following rapid advances in analytical techniques, it had become possible for biochemists to identify and to examine many new proteins. Consequently, the possibility for large-scale protein studies seemed attainable.[15] The proteome was defined as the total set of proteins expressed in a given cell at a given time, the study of which is termed 'proteomics'[16].

15 See Patterson, Scott D./Aebersold, Ruedi H., Proteomics: The First Decade and Beyond, 33 Nature Genetics Supplement 2003, 311, 314.

16 See Dove, Alan, Proteomics: Translating Genomics into Products? 17 Nature Biotechnology 1999, 233. A comprehensive glossary of biotechnological terms and definitions is provided

'Proteomics' conjures up two distinct but interdependent associations. First, it refers to the general analysis of proteins. Here, the objective is to gain insights into the composition, function and further development of protein structures. This analysis is carried out against the backdrop of the effects that protein structural changes can have on biological organisms.[17] Second, the term was coined to make an analogy with genomics, to indicate proteomics' potential to become the major "next step" of biotechnological analysis.[18] 'Proteomics' particularly focuses on the complex relations between proteins and gene sequences, taking into account that the specific function of the genome can only be determined with knowledge of the genome's product, the protein. Starting from the encoding of proteins by the genome, proteomics can therefore also be defined as the systematic study of proteins, with the aim of understanding the whole and detailed function of gene sequences.[19] Proteomics aims to provide information about (a) the conditions under which predicted gene products are translated, (b) the timing of the translation, and (c) the extent of 'post-translational' modifications, i.e. changes to the structure of proteins not *directly* related to the genetic code and the process of translation. It is worth noting that none of these elements is necessarily predicted by the nucleotide acid sequence alone.[20] Consequently, one of the major aims of proteomics is to identify the forces that determine the exact structure of gene products apart from the genetic code.[21]

It is worth mentioning that the term 'proteomics' is sometimes used differently, depending on the context. In the scientific community, it is used very broadly, encompassing everything from protein characterization techniques (such as mass spectrometry and two-dimensional gel electrophoresis) to anything remotely related to the quantitative determination of proteins. At the same time, biotechnology firms engaged in any kind of protein analyses often describe themselves as "proteomic firms", using the term as a cachet to signal attractiveness for potential investors.[22]

on the website of the "Human Genome Project Information", at http://www.ornl.gov/. See also Patterson, Scott D./Aebersold, Ruedi H., Proteomics: The First Decade and Beyond, 33 Nature Genetics Supplement, 311, 314. Hall provides a slightly modified definition of "proteomics", as "the science and technology of cataloguing and describing the behavior of all the proteins encoded in a particular organism's genome", see: Hall, Stephan S., Revitalizing Drug Discovery, Technology Review October 2003, 39, 44.

17 Patterson, Scott D./Aebersold, Ruedi H., Proteomics: The First Decade and Beyond, 33 Nature Genetics Supplement, 311, 314.

18 http://www.wikipedia.org/wiki/Protemics, last checked on January 22, 2008.

19 Patterson, Scott D./Aebersold, Ruedi H., Proteomics: The First Decade and Beyond, 33 Nature Genetics Supplement, 311, 314; Mullner, S/Neumann, T./Lottspeich, F., Proteomics–A new Way for Drug Target Discovery, 48 Arzneimittelforschung 1998, 93.

20 Humphery-Smith, I., Blackstock, W., Proteome Analysis: Genomics via the Output rather than the Input Code, 16 Journal of Protein Chemistry 1997, 537.

21 The proteomic analysis of complete complements of proteins encompasses not only the identification and quantification of proteins, but also the determination of their localization, modifications, interactions, activities, and function, see Fields, Stanley, Proteomics in Genomeland, 291 Science 2001, 122f, 122.

22 Dove, Alan, Proteomics: Translating Genomics into Products?, 17 Nature Biotechnology 1999, 233.

Finally, the term 'functional proteomics' should be introduced, as it refers to the 3-D structure determination of all proteins encoded by the genome of key organisms, a major focus of this study. The major goal of functional proteomics is the analysis of protein structures by an integrated approach combining computer-based technologies of bioinformatics and the in-depth analysis of 3-D protein structures through physical methods, such as nuclear magnetic resonance (NMR) spectroscopy or x-ray crystallography (see below).

B. Proteins and the biological organism

Proteins[23] support every aspect of biological activity.[24] Through their structural stability, diversity, and chemical reactivity, proteins influence and enable most of the key processes associated with life. They operate as catalysts[25], provide mechanical support and immune protection, transport and store other molecules such as oxygen, cause movement[26], transmit nerve impulses, and direct growth and differentiation.[27]

I. Amino acid sequences

In order to understand the functioning of proteins one must be aware that the term "protein structure" refers to three distinct levels of organization: primary, secondary, and tertiary. The primary structure refers to the amino acid sequence as such. The secondary structure describes the conformation or spatial relationship adopted by local regions of the polypeptide chain. Finally, "tertiary structure" expresses the entire folding of the polypeptide chain.[28]

23 The origin of the word "protein" is usually attributed to Jöns Jakob Berzelius (1779-1848) and has been ascribed to derivation from the Latin word primarius, or from the Greek word for "first thing" (in Greek πρωτεΐνη = first element), see Whitford, David, Proteins – Structure and Function, Chichester, West Sussex, England, 2005, 1.

24 Whitford, David, Proteins: Structure and Function, Chichester, West Sussex, U.K., 2005, 9.

25 The term catalyst refers to substances that accelerate chemical reactions.

26 Schwaiger, Ingo/Sattler, Clara/Hostetter, Daniel R./Rief, Matthias, The Myosin coiled-coil is a truly elastic Protein Structure, 1 Nature Materials 2002, 232.

27 Berg, Jeremy M./Tymoczko, John L./Stryer Lubert, Biochemistry, New York, NY, 2005, 41.

28 Whitford, David, Proteins: Structure and Function, Chichester, West Sussex, U.K., 2005, 81. The term "quaternary structure" further refers to a certain association of multiple 3-D folded proteins to form multi-subunit complexes.

1. Primary structure

All natural proteins are composed of the same set of 20 amino acids.[29] Each amino acid is constructed with a central tetrahedral carbon atom connected to an amino group, a carboxylic acid group, a distinctive side chain, and a hydrogen atom. The side chains of the 20 amino acid building blocks vary tremendously in size, shape, and the presence of functional groups. Amino acids can be grouped as follows: (1) aliphatic side chains: glycine, alanine, valine, leucine, isoleucine, methionine, and proline; (2) aromatic side chains: phenylalanine, tyrosine, and tryptophan; (3) hydroxyl-containing aliphatic side chains: serine and threonine; (4) sulfhydryl-containing cysteine; (5) basic side chains: lysine, arginine, and histidine; (6) acidic side chains: aspartic acid and glutamic acid; and (7) carboxamide-containing side chains: asparagine and glutamine. These groups are somewhat arbitrary and many other assemblies are possible.[30]

Overall, the bonds between amino acids are described as the primary structure of the protein. These bonds have several important characteristics. First, they are resistant to hydrolysis[31], so that proteins are kinetically remarkably stable. Second, the peptide group is planar because the C-N bond has a significant double-bond character. Third, each peptide bond has both a hydrogen-bond donor (the NH group) and a hydrogen-bond acceptor (the CO group). Hydrogen bonding between these backbone groups is a distinctive feature of protein structure. Ultimately, the peptide bond is uncharged, which allows proteins to form tightly packed globular structures having significant amounts of the backbone buried within the protein interior. Because they are linear polymers, proteins can be described as sequences of amino acids. Such sequences are written from the amino to the carboxyl terminus.[32] The complete amino acid sequences of more than 100,000 proteins are now known and documented. The primary structure can be illustrated as follows:[33]

29 Berg, Jeremy M./Tymoczko, John L./Stryer Lubert, Biochemistry, New York, NY, 2005, 53.

30 Berg, Jeremy M./Tymoczko, John L./Stryer Lubert, Biochemistry, New York, NY, 2005, 71-72.

31 Hydrolysis is a chemical process by which water reacts with a compound to produce other compounds. Specifically, a bond is split, and the hydrogen cation and the hydroxide anion of the water are added.

32 Berg, Jeremy M./Tymoczko, John L./Stryer Lubert, Biochemistry, New York, NY, 2005, 72.

33 Based on figure provided by National Human Genome Research Institute, Talking Glossary of Genetic Terms, available at: http://www.genome.gov/Pages/Hyperion//DIR/VIP/Glossary/Illustration/ amino_acid .shtml, last checked on October 16, 2005.

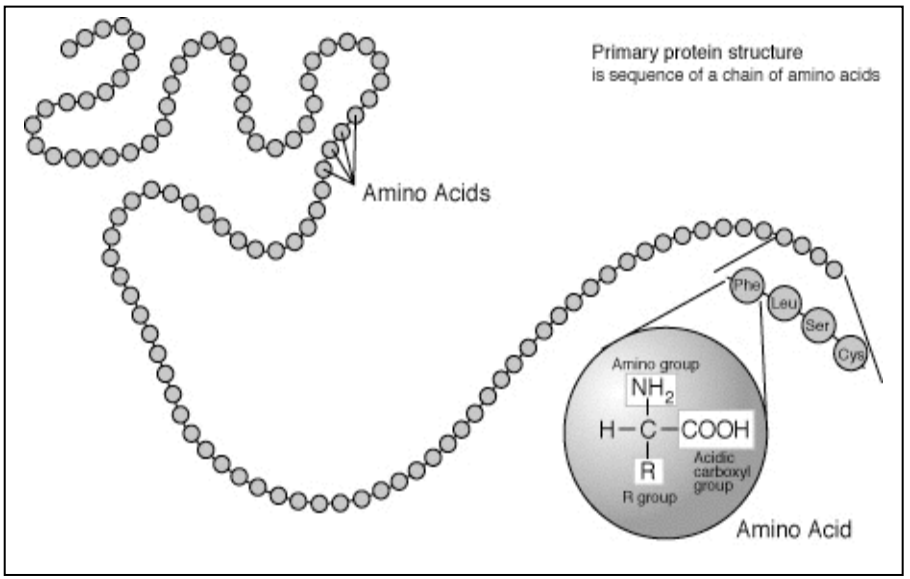

Figure 1: Primary protein structure

2. Secondary structure

As to the secondary structure, a spatial arrangement of amino acid residues exists in proximity to the sequence. Parts of the amino acid sequence are linked through hydrogen bonds. Polypeptide chains can fold into regular structures such as the α-helix, the beta sheet, and turns and loops. Two major forms of secondary structure are the α- and the β-strand. In the α-helix, the polypeptide chain is stabilized as a tightly packed rod. Within the helix, the CO group of each amino acid is hydrogen bonded to the NH group of the amino acid's four residues along the polypeptide chain. In the β-strand, the polypeptide chain is almost fully extended rather than being tightly wound as in the α-helix. Two or more β-strands linked by NH-to-CO hydrogen bonds unite to form β-sheets.

Most proteins have compact, globular shapes, requiring reversals in the direction of their polypeptide chains. Many of these reversals consist of a common structural element called the reverse turn. In many reverse turns, the CO group of residue *i* of a polypeptide is hydrogen bonded to the NH group of residue $i + 3$. This interaction adjusts to abrupt changes in the direction of the polypeptide chain. In other cases, structures that are more elaborate are responsible for chain reversals.

These structures are called loops, reflecting their overall shape. Unlike α-helices and β-strands, loops do not consist of regular, periodic structures. However, loop structures are often rigid and well defined. Turns and loops are consistently found on the surfaces of proteins and thus often play an important role in interactions between proteins and other molecules. The protein compound complex is typically the major focus of research related to drug development. Drug design only succeeds if the administered pharmaceuticals efficiently bind to the targeted protein. The commonly occurring secondary structure of a β-sheet can be illustrated as follows:[34]

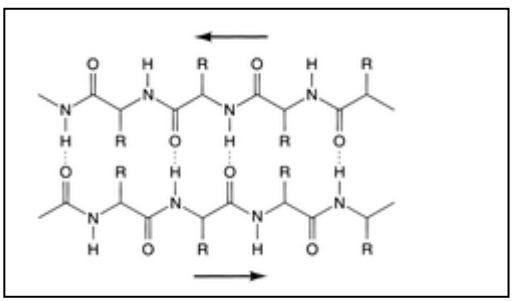

Figure 2: Secondary Structure of a β-sheet

3. Tertiary structure

The tertiary structure is the single most important determinant of the protein's biological function.[35] It refers to the folding of the basic protein, which is stabilized by interactions between the amino acid side chains on a single polypeptide forming the three dimensional molecule. Water-soluble proteins fold into compact structures with a nonpolar interior. Their asymmetric structures have two properties in common: (1) a core built of amino acids with hydrophobic side chains and (2) a surface formed largely of hydrophilic amino acids that interact with the aqueous[36] environment. The leading force behind the formation of the tertiary structure of water-soluble proteins is the hydrophobic interaction between the interior residues. Some proteins that exist in a hydrophobic environment in membranes display the inverse distribution of hydrophobic and hydrophilic amino acids. Within those proteins, the hydrophobic amino acids are on the surface to interact with the environment, whereas the hydrophilic groups are shielded from the environment in the interior of the protein.

34 Based on a figure provided by Wikipedia, available at: http://en.wikipedia.org/wiki/Beta_sheet, last checked on January 21, 2008.
35 Whitford, David, Proteins: Structure and Function, Chichester, West Sussex, U.K., 2005, 39.
36 A solution in which the solvent is water.

The folding of most proteins is complex and devoid of symmetry. A unifying principle becomes apparent from the distribution of side chains. The physical analysis of myoglobin[37] provided the first 3-D picture of a protein. Many of the basic rules governing tertiary structure rely on this discovery. In myoglobin, approximately 70% of the main chain is folded into eight α-helices and much of the remaining amino acids form turns and loops between helices. The interior consists almost entirely of nonpolar residues such as leucine, valine, methionine, and phenylalanine. Charged residues such as aspartate, glutamate, lysine, and arginine are absent from the inside of myoglobin. Only two polar residues reside inside the protein. Both are histidine residues and play critical roles in binding iron and oxygen. The outside of myoglobin consists of both polar and nonpolar residues.[38] There are approximately 200 different structures, including mutants of myoglobin.[39] Meanwhile, physical proteomics technologies, such as hX-ray crystallography and NMR approaches described below, have revealed the detailed three-dimensional structures of thousands of proteins.[40] To understand the protein's function, it is of fundamental importance to define the 3-D folding type.[41] An illustration of the 3-D folding structure of myoglobin is shown in Figure 3[42]:

37 The protein myoglobin is the oxygen carrier in muscles.

38 Polypeptides containing more than one polypeptide chain exhibit a fourth level of structural organization ("Quaternary structure"). Each polypeptide chain in such a protein is called a subunit. Quaternary structure describes the spatial arrangement of subunits and the nature of their interaction and can be as simple as two identical subunits or as complex as dozens of different subunits. In most cases, the subunits are held together by noncovalent bonds. One identical subunit organization is present in the DNA-binding protein CRo found in a bacterial virus called λ. A more complicated quaternary structure is human hemoglobin, the oxygen-carrying protein in blood, which consists of two subunits of one type and two subunits of another type. See Berg, Jeremy M./Tymoczko, John L./Stryer Lubert, Biochemistry, New York 2002, 63-64.

39 Whitford, David, Proteins: Structure and Function, Chichester, West Sussex, U.K., 2005, 68.

40 Whitford, David, Proteins: Structure and Function, Chichester, West Sussex, U.K., 2005, 346.

41 Matthias Mann, director of the Center for Experimental BioInformatics (CEBI) at the University of Southern Denmark, in his opening remarks at the HUPO 4th Annual World Congress, "From defining the proteome to understanding the function", held from August 29 to September 1, 2005 in Munich.

42 The figure is based on the represenatation provided by Wikipedia, available at http://en.wikipedia.org/wiki/Protein, last checked on January 21, 2008. Myoglobin was the the first protein structure revealed by X-ray crystallography. Max Perutz and Sir John Cowdery Kendrew discovered its structure in 1958; both men later received the Nobel Prize in Chemistry.

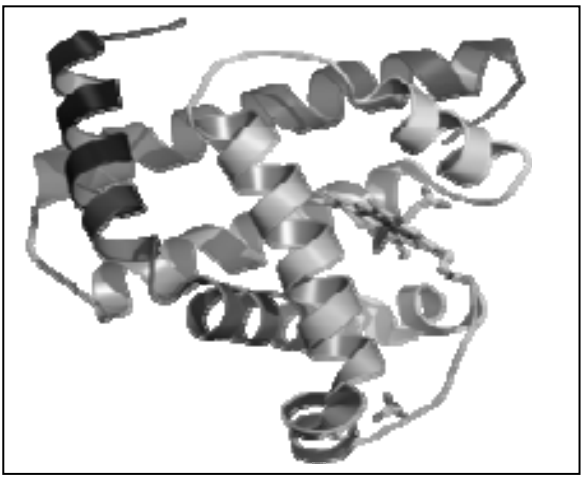

Figure 3: 3-D folding structure of myoglobin

III. Protein folding

1. Folding funnel theory of protein folding

How is a protein able to fold reliably into a predictable conformation? How can the mechanism be described in which the protein is carried from its unfolded random coil to a uniquely folded metastable state? Biochemical studies found that denatured proteins have all of their native three-dimensional structure disrupted. Yet, many of them refold efficiently and completely recover their biological activity when placed under conditions in which the folded form of the protein is stable.[43] Therefore, it is assumed that a native protein exists in some kind of thermodynamic configurational equilibrium. The biologically active state is the one with the lowest configurational energy.[44] The sequence of events guiding the protein folding is called the "protein folding pathway".[45] A random search among the entire conformation space for conformers would require an enormously long time.[46] Proteins, however, are able to

43 Berg, Jeremy M./Tymoczko, John L./Stryer Lubert, Biochemistry, New York, NY, 2005, 72-73.

44 Levinthal, Cyrus, Are there Pathways for Protein Folding? 65 Journal de Chimie Physique 1968, 44, 44.

45 Levinthal, Cyrus, Are there Pathways for Protein Folding?, 65 Journal de Chimie Physique 1968, 44, 44.

46 Although the protein is able to sample new configurations very fast, it will take at least 1027 years to try them all, see Zwanzig, R./Szabo, A./Bagchi, B., Levinthal's paradox, 89 Proceed-

fold within milliseconds to seconds. This implies that only a small amount of conformation space is sampled during the folding process. The problem of how proteins fold rapidly into their three-dimensional conformation despite the infinite number of possible configurations is described as the *Levinthal-Paradox*.[47] Each bond connecting amino acids can occur in several possible states.[48]

Several models attempt to explain the phenomenon of protein folding. A more recent model approaches the issue through a so-called "folding funnel" theory.[49] The conformational energy surface of a protein folding pathway is graphically displayed as a funnel. Convergent kinetic pathways guide the folding to a unique, stable, native conformation.[50] It is assumed that the random polypeptide chain first collapses in a dense structure. Native bonds emerge when fluctuation of the peptide chain randomly associates distant polypeptide sequences. Each native conformation stabilizes the chain and simultaneously narrows the conformational space. Thus, the random search for all further native conformations occurs more rapidly. Through the gradual native configuration, the peptide chain is efficiently transformed into its three-dimensional structure.

As already mentioned, the collapse of the primary amino acid structure into the tertiary folding state can be illustrated through an energy landscape that has the image of a folding funnel. The wide rim demonstrates the multitude of accessible conformation pathways that exist initially. The narrow bottom shows the minimum of configuration flexibility, which mirrors the final state.[51] Each protein follows a different folding path as it approaches its specific native structure. The exact nature of

ings of the National Academy of Science of the United States of America 1992, 20-22; Nienhaus, Ulrich, Physik der Proteine, 3 Physik Journal 2004, 37, 39.

47 Nienhaus, Ulrich, Physik der Proteine, 3 Physik Journal 2004, 37, 39; Zwanzig, R./Szabo, A./Bagchi, B., Levinthal's paradox, 89 Proceedings of the National Academy of Science of the United States of America 1992, 20-22; Levinthal, Cyrus, Are there Pathways for Protein Folding?, 65 Journal de Chimie Physique 1968, 44-45.

48 Whitford, David, Proteins: Structure and Function, Chichester, West Sussex, U.K., 2005, 403-404.

49 Onuchic, J. N./Luthey-Schulten, Z./Wolynes, P. G., Theory of Protein Folding: The Energy Landscape Perspective, 48 Annual Revue of Physical Chemistry 1997, 545; Leopold, E. Peter/Montal, Mauricio/Nelson ONuchic, José Nelson, Protein Folding Funnels: A Kinetic Approach to the Sequence-structure Relationship, 89 Proceedings of the National Acadamy of Science of the United States of America 1992, 8721; Nienhaus, Ulrich, Physik der Proteine, 3 Physik Journal 2004, 37, 39.

50 Leopold, E. Peter/Montal, Mauricio/Nelson ONuchic, José Nelson, Protein Folding Funnels: A Kinetic Approach to the Sequence-structure Relationship, Proceedings of the National Acadamy of Science of the United States of America 1992, 8721, 8721.

51 Nienhaus, Ulrich, Physik der Proteine, 3 Physik Journal 2004, 37, 39-40.

these differences depends on the protein's size, stability, and structure.[52] Figure 4 illustrates this process:[53]

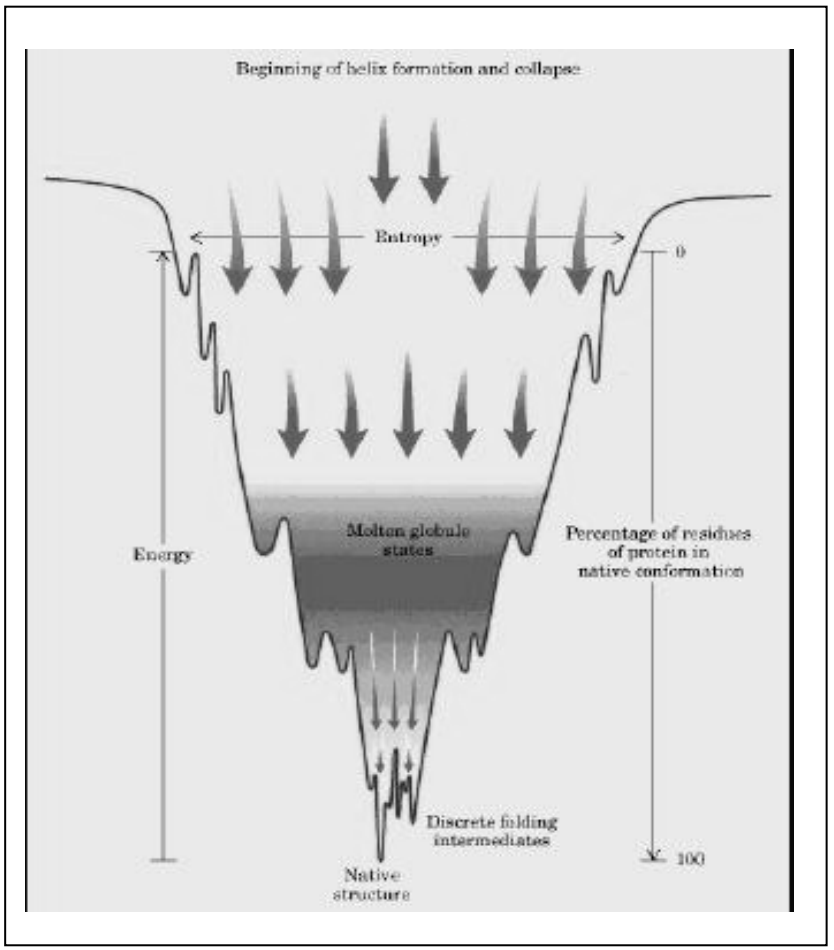

Figure 4: Energy landscape of a protein

52 For a statistical energy landscape approach that explains when and why certain processes such as specific folding pathways occur in some proteins, see Bryngelson, J. D./Onuchic, J. N./Socci, N. D./Wolynes, P. G., Funnels, Pathways, and the Energy Landscape of Protein Folding: A Synthesis, 21 Proteins 1995, 167-195.

53 Based on a figure from Kavraki, Lydia E., Protein folding, available at http://cnx.org/content/m11467/latest/.

2. Protein misfolding and diseases arising from 'folding' defects

With a better understanding of folding, scientists realized that diseases arise because of misfolding.[54] Already small structural defects can give rise to a wide range of folding diseases. Genetic diseases, such as cystic fibrosis and sickle cell anemia, are typically caused by mutations within coding regions.[55] Protein misfolding also plays a crucial role in the pathogenesis of prion diseases.[56] A prion is a protein part that lacks nucleic acid.[57] Normally, it occurs in a harmless form, but its misfiled variation has been identified as the cause of various neurodegenerative disorders such as scrapie, bovine spongiform encephalopathy (BSE, its human equivalent, the Creutzfeld-Jakob disease (CJD), and Kuru. The progression of these diseases is accompanied by the appearance of insoluble protein plaques in the brain (amyloid plaques).[58] The specific protein that has been isolated from the protein plaque is the PrP protein, which has the ability to exist in two stable forms, PrP-C and PrP-Sc. The sequences of PrP-C and PrP-Sc are found to be identical. Biochemical researchers discovered that the brain plaques contain PrP-Sc. All experiments showed that the Prp-Sc was not from an external source, but expressed by the host cell itself. This form of the protein was the only cause of infection in the prion diseases. The disease-specific feature is consequently not the expression of the prion protein, but rather its biophysical and biochemical characteristics. A purely structural change is assumed to cause its aggregation in the brain.[59] The ability of PrP to exist in two stable forms and the fact that the disease-specific feature does not depend on the genetic coding

54 Whitford, David, Proteins: Structure and Function, Chichester, West Sussex, U.K., 2005, 426.

55 Whitford, David, Proteins: Structure and Function, Chichester, West Sussex, U.K., 2005, 426.

56 Tatzelt, Jorg/Winklhofer, Konstanze F., Folding and Misfolding of the Prion Protein in the Secretory Pathway, 11 Amyloid 2004, 162-172.

57 The term 'prion' is derived from 'proteinaceous infectious particle, see Whitford, David, Proteins: Structure and Function, Chichester, West Sussex, U.K., 2005, 431. For a definition, see Medline Plus, Medical Dictionary, available at: http://www.nlm.nih.gov/medlineplus/mplusdictionary.html, last checked on January 21, 2008.

58 Scarpie occurs in sheep and leads to a progressive loss of motoric coordination, finally ending in an inability to stand unsupported. It was first identified in the 17th century in the United Kingdom, with similar forms discovered more recently in other animals, such as mink, deer and elk. CJD typically occurs in humans above 50 years of age. Infected persons exhibit dementia and loss of motoric coordination. CDJ was first described in the 1920s. Kuru or 'the laughing dead' occurred in the 1960 in the Highlands of Papua New Guinea, where the conduct of cannibalism was held to be responsible for the progression of the disease. A decline in cannibalism resulted in a decline in Kuru, although the precise agent has yet not been identified, as described in Whitford, David, Proteins: Structure and Function, Chichester, West Sussex, U.K., 2005, 433. For the potential causes of scarpie, see also Prusiner, Stanley B., Novel Proteinaceous Infectious particles cause scrapie, 216 Science 1982, 136.

59 Tatzelt, Jorg/Winklhofer, Konstanze F., Folding and Misfolding of the Prion Protein in the Secretory Pathway, 11 Amyloid 2004, 162, 162.

seems contrary to the long-held hypothesis that an amino acid codes for a single unique 3-D structure.[60] Amyloid plaques or protein aggregations in the brain are also associated with Alzheimer's disease and Parkinson's disease, conditions not considered prion-based but also dependent on aberrant protein folding.[61] The primary structure does not absolutely determine the tertiary folding structure. It is now widely believed that gene expression alone largely, but not exclusively, controls the protein's 3-D properties.

III. Structurally similar, sequence dissimilar proteins

With the discovery of increasingly more protein structures, it has further become evident that many proteins that possess similar structures share only a very small number of identical residues in structurally associated positions.[62] Various structurally similar protein pairs have only a minimal amount of sequence identity. This suggests that many sequence positions do not play a significant role in structure determination, and folding determinants are restricted to a limited number of sequence residues.[63] Structurally similar proteins do therefore not necessarily reflect sequence-similar proteins.[64] Some proteins bearing diverse sequences with essentially no sequence homology, do fold into the same structure. With the protein's effect depending on the structure, large numbers of different proteins are able to perform the same functions.[65]

IV. Posttranslational modifications (PTM)

An important component of protein regulation and function is the modification of protein structures, which occur either co- or posttranslationally. Translation refers to

60 Tatzelt, Jorg/Winklhofer, Konstanze F., Folding and Misfolding of the Prion Protein in the Secretory Pathway, 11 Amyloid 2004, 162, 166.

61 Tatzelt, Jorg/Winklhofer, Konstanze F., Folding and Misfolding of the Prion Protein in the Secretory Pathway, 11 Amyloid 2004, 162, 162.

62 Jaenichen, Hans-Rainer/Mcdonell, Leslie A./Haley, James F., Jr., From Clones to Claims, Cologne, Berlin, Bonn, Munich 2002, 167; molecular biologists thus attempted to identify the common hidden information within these sequences that directs them to assume similar folds.

63 Kleist, Peter, Biomarker und Surrogat-Endpunkte: Garanten für eine schnellere Zulassung von neuen Arzneimitteln?, 83 Schweizerische Ärztezeitung 2022, 2347, 2350.

64 Wachenfeld, Joachim, The Patenting of Protein Structures, http://www.vossiusandpartner.com/eng/publication/mip-yearbook.html 2002.

65 Structural protein families are also called 'protein superfamilies'; see: Hultquist, Steven J./Robert Harrison, and Yongzhi Yang, Patenting Bioinformatic Inventions: Emerging Trends in the United States, 20 Nature Biotechnology 2002, 743; 771. A list of protein superfamilies with structure-based-sequence-alignment is available at: http://www-cryst.bioc.cam.ac.uk/~campass/superfamily.html, last checked on May 06, 2005.

the process in which the genetic code carried by mRNA directs the synthesis of proteins from amino acids.[66] Through constant modification of the protein, organisms accommodate radically different protein expression in different parts of the body and in different stages of the life cycle. Although amino acids can be predicted from nucleotide sequences, posttranslational modifications to proteins, in general, cannot.

Once synthesized on the ribosomes, proteins are subject to a multitude of modification steps. Because they are cleaved (thus eliminating signal sequences, transit or pro-peptides and initiator methionines), many simple chemical groups (for example acetyl, methyl, phosphoryl) as well as more complex molecules (such as sugars and lipids) can associate with them. Moreover, they can be internally or externally cross-linked (example: disulfide bonds). So far, over 200 different modifications have been described. The complexity due to all these modifications is compounded by the high level of diversity that alternative splicing[67] can produce at the level of the sequence. Many PTM have well described roles in signal transduction and the regulation of cellular processes. In contrast, other modifications are much less well documented but are also likely to play very important roles within the cell. Identifying the type and location of these proteins is a first step in understanding their regulatory potential. The complex study of posttranslational modifications is one major objective of proteomics and is referred to as 'PTM proteomics'. [68]

V. Role of Enzymes and their chemical activity

One important function performed by proteins is the ability to catalyze chemical reactions.[69] The biological catalysts were named enzymes.[70] Enzymes are usually specific to the reaction they catalyze and the chemical substances involved in the reaction. Many enzymes are composed of several proteins acting together as a unit.

66 Human Genome Project Information, Glossary of the Human Genome Project, available at http://www.ornl.gov/TechResources/Human_Genome/glossary/. Recent advances in mimicking PTMs are helping to elucidate the role of the modifications and are the subject of high expectations for future pharmaceuticals, Davis, Benjamin G., Mimicking Posttranslational Modifications of Proteins, 303 Science 2004, 480.

67 Alternative splicing of mRNA permits that many gene products with different functions are produced from a single coding sequence, see Brett, David/Pospisil, Heike et al., Alternative splicing and genome complexity, Nature Genetics 30, 2 (2001).

68 MacCoss, Michael J./Hayes McDonald; Saraf,/Saraf, Anita/Sadygov, Rovshan/Clark, Judy M./Tasto, Joseph J./Gould, Kathleen L./Wolters, Dirk/Washburn, Michael/Weiss, Avery/Clark, John I./Yates, John R., Shotgun Identification of Protein Modifications from Protein Complexes and Lens Tissue, 99 Proceedings of the National Academy of Science of the United States of America 2002, 7900, 7901.

69 Catalytic function was amongst the first biological roles recoginzed in proteins through the work of Eduard Buchner and Emil Fischer., Whitford, David, Proteins: Structure and Function, Chichester, West Sussex, U.K., 2005, 189.

70 The name derived from the Greek for 'in yeast' - 'en' 'zyme', Whitford, David, Proteins: Structure and Function, Chichester, West Sussex, U.K., 2005, 189.

Most parts of an enzyme have regulatory or structural functions. The catalyzed reaction takes place in only a small part of the enzyme called the active site. It is determined by a 3-D cleft formed by groups originating from different parts of the amino acid sequence. The active site, also described as a "binding pocket", takes up a relatively small part of the total volume of the enzyme.

Enzyme-substrate binding was historically described through the "lock-and-key model". The binding depends on the precisely defined arrangements of atoms in an active site. Complementary structural properties of the enzyme and substrate are responsible for this specificity. Most enzymes are highly selective with respect to the substrates that they bind, since their catalytic specificity depends partly on the specificity of binding. The active site contains the residues directly involved in the breaking and formation of bonds. These residues are referred to as catalytic groups. The catalytic power of enzymes originates from their ability to unite substrates in favorable orientations so as to promote the formation of the transitional states in enzyme-substrate complexes.[71] In 1958, Daniel Koshland introduced the "induced fit model", a modification of the lock and key model. It is based on the understanding that enzymes are flexible structures, in which the active side is continuously reshaped by its interaction with the substrate. Consequently, the amino acid side chains constituting the active side are molded into the exact position to start the catalytic function of the enzyme.[72] The enzyme-substrate complex according to the "induced fit model" is illustrated in Figure 5:[73]

71 Berg, Jeremy M./Tymoczko, John L./Stryer Lubert, Biochemistry, New York, NY, 2005, 200; Wikipedia, Enzymes, available at http://en.wikipedia.org/wiki/Image:Two_substrates_b.png, last checked on January 22, 2008.

72 Koshland D. E., Application of a Theory of Enzyme Specificity to Protein Synthesis, Proceedings of the National Academy of Science 44 (2), (1958), 98.

73 Based on Figure 5 provided by Wikipedia, Enzymes, available at: http://en.wikipedia.org/wiki/Imag e: Two_substrates_b.png, last checked on January 22, 2008.

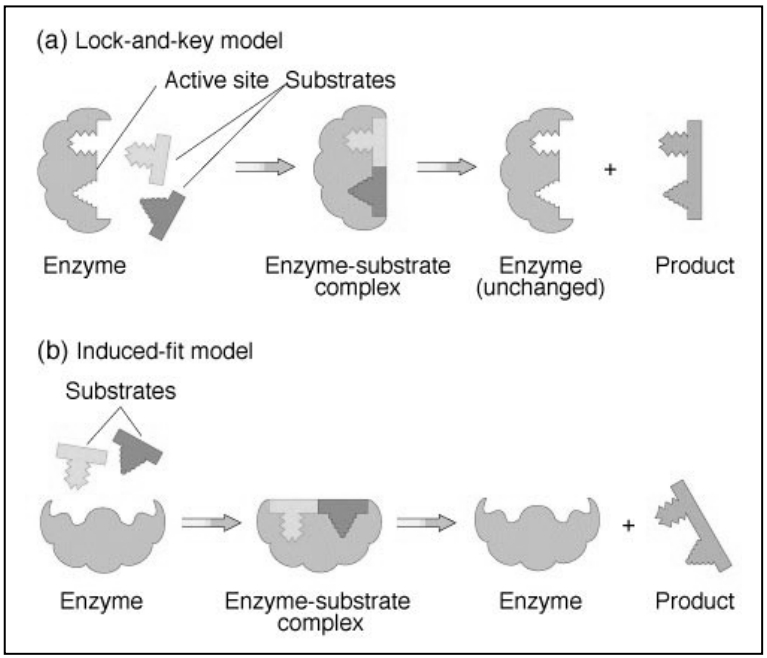

Figure 5: Enzyme-substrate complex

The primary function of enzymes is to enhance rates of reaction. Thereby they are compatible with the needs of the organism. Chemical reactions require a certain amount of activation energy to take place. Enzymes can increase the reaction speed by favoring or enabling a different reaction path with lower activation energy, making it easier for the reaction to occur. They can also serve to associate two or more reactions together, such that a thermodynamically favorable reaction can be used to "drive" a thermodynamically unfavorable one. The most common examples are enzymes that use the dephosphorylation of ATP to drive some otherwise unrelated chemical reactions.[74] Enzymes conduct up to several million catalytic reactions per second. In order to understand how enzymes work, a kinetic description of their activity is used. The maximum speed of an enzymatic reaction is determined by the so called "Michaelis-Menten equation". Here, the substrate concentration is increased until a constant rate of product formation is achieved. This is the maximum velocity (V_{max}) of the reaction catalyzed by the enzyme. In this state, all enzyme active sites are saturated with substrate. Since the substrate concentration at V_{max} cannot be precisely determined, enzymes are characterized by the substrate concentration at which

74 Figure available at http://lc.brooklyn.cuny.edu/smarttutor/core3_21/energy.html, last checked on January 22, 2008.

the rate of reaction is half its maximum. This substrate concentration is called the Michaelis-Menten constant (K_M).[75]

The activities of many enzymes can be anticipated by the binding of specific small molecules and ions. Inhibitor activity serves as a major control mechanism in biological systems. Many drugs act in this fashion. Inhibition by specific substrates can give a valuable insight into the mechanism of enzyme action. Enzyme inhibition occurs either reversibly or irreversibly. An irreversible inhibitor disconnects slowly from its target enzyme, because it binds tightly to it. Some important drugs are irreversible inhibitors. Penicillin acts by modifying the enzyme and thereby inhibiting the synthesis of bacterial cell walls, thus killing the bacteria. Aspirin has the ability to suppress the production of prostaglandins and thromboxanes by enzyme modification.[76]

Reversible inhibition, in contrast, describes the rapid dissociation of the enzyme-inhibitor complex. By competitive inhibition, an enzyme is not only bound by its natural substrate, but also by a further substrate ("inhibitor") which does not trigger the catalytic reaction. In this way, further binding of the natural substrate and its subsequent reaction are inhibited. The competitive inhibitor is similar to the substrate and associates to the active center of the protein. Thus, it prevents the substrate from binding to the same active site and diminishes the rate of catalysis by reducing the proportion of enzyme molecules bound to a substrate. Increasing substrate concentration leads to a decrease of competitive inhibitions.[77] Competitive inhibition[78] and non-competitive inhibition[79] are illustrated in Figures 6 and 7:

75 Berg, Jeremy M./Tymoczko, John L./Stryer Lubert, Biochemistry, New York, NY 2005, 200-203.

76 Prostaglandins are hormone-like substances, which are produced in the body and have various effects, including the transmission of pain information to the brain, modulation of the hypothalamic thermostat, and inflammation. Thromboxanes act to promote the aggregation of platelets that form blood clots. The effects of aspirin were discovered in 1971 by the British pharmacologist, John R. Vane. He was awarded a Nobel Prize in Physiology and Medicine for his research in 1982. Berg, Jeremy M./Tymoczko, John L./Stryer Lubert, Biochemistry, New York, NY 2005, 209.

77 For a detailed overview of the specific chemical procedures see Berg, Jeremy M./Tymoczko, John L./Stryer Lubert, Biochemistry, New York, NY, 2005, 209-219.

78 See: http://en.wikipedia.org/wiki/Enzyme, last checked on January 22, 2008.

79 The diagram showing the mechanism of non-competitive inhibition is taken from Wikipedia http://en.wikipedia.org/wiki/Enzyme, last checked on January 21, 2008.

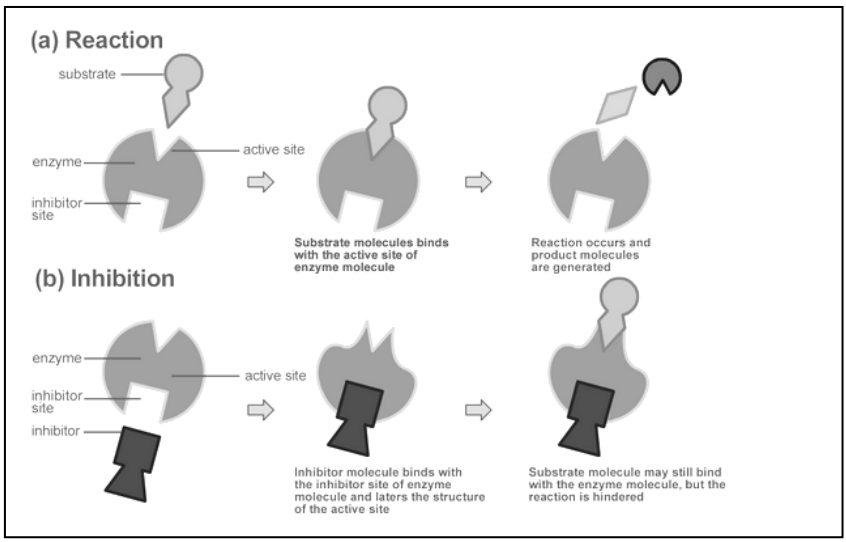

Figure 6: Competitive inhibition

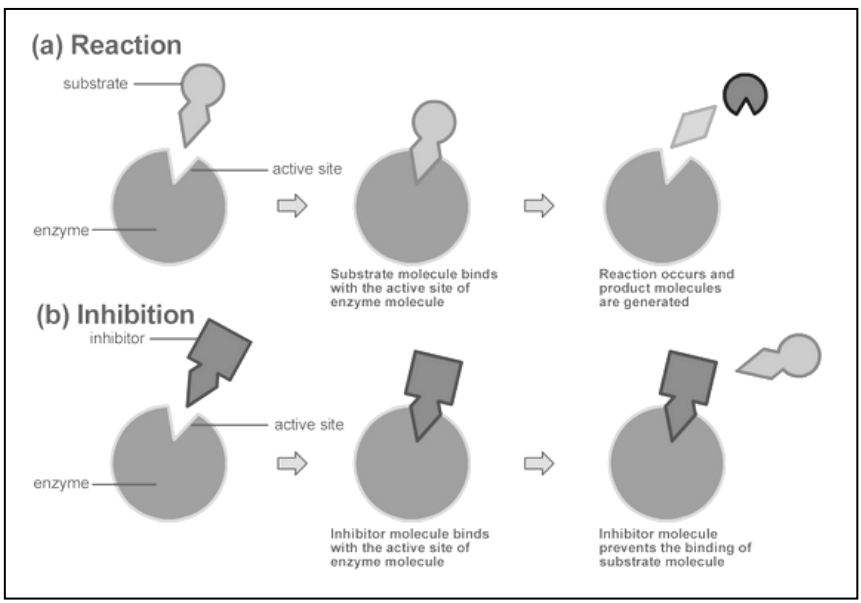

Figure 7: Non-competitive inhibition

C. Genetic coding of proteins[80]

In order to produce a protein, a cell requires information about the sequence in which the amino acid must be assembled.[81] The cell utilizes a long polymeric molecule, DNA (deoxyribonucleic acid), to store this information. The amino acid sequence of a protein is genetically determined by the sequences of bases in a DNA molecule. The subunits of the DNA are called nucleotides.[82] DNA encompasses four nucleotides that are distinguishable from the base regions of the molecule. The four bases are adenine, guanine, cytosine, and thymine (referred to as A, G, C and T). The sequence of these bases along the DNA molecule determines which amino acids will be inserted in sequence into the polypeptide chain of a protein. DNA is synthesized in extremely long strands (called chromosomes) encompassing information encoding for the sequence of many proteins. The region of DNA on the chromosome that determines the sequence of a single protein is called a gene.[83] The process in which the data in a gene is utilized to synthesize a new protein is called gene expression. To express a gene, a copy of the gene as a molecule of RNA (ribonucleic acid) is made. RNA is a molecule very similar to DNA. One difference, however, is that RNA contains a different sugar (ribose instead of deoxyribose). Furthermore, the base thymine (T) of DNA is replaced in RNA by the structurally similar base, uracil (U).[84] The process of making an RNA copy of DNA is called transcription.[85] The transcribed RNA copy contains sequences of A, U, C, and G having the same information as the sequence of A, T, C and G in the DNA. The RNA molecule, referred to as messenger RNA (mRNA), then progresses to a location in the cell where proteins are synthesized. The information encoding the sequence of amino acids in a protein (the "genetic code") is composed of serially reaching groups of three contiguous nucleotides. Each combination of three contiguous nucleotides, called a codon, determines one amino acid. The four bases A, G, C and U can be specified as triplets in 64 different ways, but there are only 20 amino acids to be translated. Thus,

80 Alberts, Bruce/Johnson, Alexander/Lewis, Julian, Molecular Biology of the Cell (4th ed.), New York 2002, 111-112.

81 CAFC decisions often provide a useful and clear illustration of the scientific background. The process of genetic coding and translation is explained in: In re O'Farrell 853 F.2d 894, 895-899 (Fed. Cir. 1988); for a detailed overview of the genetic coding of proteins see Vossius, Volker/Jaenichen, Hans-Rainer, Zur Patentierung biologischer Erfindungen nach Europäischem Patentübereinkommen und Deutschem Patentgesetz - Formulierung und Auslegung von Patentansprüchen, GRUR 1985, 821.

82 Alberts, Bruce/Johnson, Alexander./Lewis, Julian, Molecular Biology of the Cell, New York 2002, 98.

83 For a brief overview of the basics of genetics, see also Kraßer, Rudolf, Patentrecht: ein Lehr- und Handbuch zum deutschen Patent- und Gebrauchsmusterrecht, europäischen und internationalen Patentrecht, 5. Aufl., München 2004, 222.

84 Alberts, Bruce/Johnson, Alexander./Lewis, Julian, Molecular Biology of the Cell, New York 2002, 104-105.

85 Alberts, Bruce/Johnson, Alexander./Lewis, Julian,Molecular Biology of the Cell, New York 2002, 104.

most amino acids are encoded by more than one codon. In addition, three codons exist which do not encode any amino acid. They are called 'stop codons'.[86] Complicated cellular machinery is involved in the synthesis of proteins. Complexes of more than fifty different proteins associated with several structural RNA molecules (rRNAs), are called ribosomes.[87] These molecules 'read' the necessary information in the messenger RNA molecule, shift three nucleotides along the strand of RNA at a time, and add the amino acid determined by the codon to a growing polypeptide chain. When it arrives at a stop codon, the polypeptide chain is complete and detaches from the ribosome. This process of synthesizing a new polypeptide chain from the genetic information contained on the messenger RNA molecule with the aid of ribosomes is referred to as translation.[88] The messenger RNA can be used to synthesize many copies of the same protein. The translation of messenger RNA starts at the particular sequence of nucleotide that binds the RNA to the ribosome. The translation then continues by reading nucleotides, three at a time, until a stop codon is read. Reading errors might lead to entirely different peptides, most likely useless ones.[89]

D. Recombinant Protein Synthesis

If a human gene is transferred into a bacterium, this bacterium is able to synthesize the human protein.[90] The method of producing large quantities of identical copies of a gene by integrating it into prokaryotic cells and then replicating those cells is referred to as "DNA-cloning".[91] After having produced a significant amount of the

86 Alberts, Bruce/Johnson, Alexander./Lewis, Julian, Molecular Biology of the Cell, New York 2002, 106.

87 Alberts, Bruce/Johnson, Alexander./Lewis, Julian, Molecular Biology of the Cell, New York 2002, 107.

88 Alberts, Bruce/Johnson, Alexander./Lewis, Julian, Molecular Biology of the Cell , New York 2002, 106.

89 Alberts, Bruce/Johnson, Alexander./Lewis, Julian, Molecular Biology of the Cell, New York 2002, 107.

90 Human beings, animals, and plants are classified as eukaryotic organisms: their DNA is enclosed in chromosomes in a special part of the cell, the nucleus. In contrast, Bacteria (prokaryotic organisms) have a different organization. Their DNA is not included in a separate nucleus. Irrespective of the large differences between them, all organisms, whether eukaryotic or prokaryotic, encode proteins pursuant to the same rules that govern genes. While most commercially valuable proteins come from human beings or other eukaryotes, bacteria can be grown in huge amounts. Therefore, one strategy for producing a preferable protein is to shift the gene carrying the protein's information from the eukaryotic cell, where the gene normally occurs, into a bacterium. Bacteria bearing genes from a foreign source (heterologous genes) integrated into their own genetic machinery are said to be transformed. When transformed bacteria grow and divide, the integrated heterologous genes are replicated. It is possible to synthesize large amounts of transformed bacteria that encompass transplanted heterologous genes, see In re O'Farell, 853 F.2d 894, 898 (Fed. Cir. 1988).

91 Brown, Terence A., Gentechnologie für Einsteiger, Berlin 2002, 4-5.

transformed bacteria, it is stimulated to express the cloned gene and to make useful quantities of the protein. To make a particular protein by expressing its cloned gene in bacteria (referred to as 'a recombinant process')[92] several steps must be performed.[93] First, the gene coding for the particular protein has to be isolated. Next, the isolated genes must be transferred to the host bacterium. This is typically performed by incorporating the gene into a cloning vector. A cloning vector is a portion of DNA that can be integrated into bacteria and that replicates itself each time the bacteria divide. A frequently used type of cloning vector is referred to as plasmid. A plasmid is a small circular loop of DNA originating in bacteria, which exists separately from the chromosome. Due to their small size, they can easily be isolated. Recombinant DNA technology can be used to modify plasmids. Such a modified plasmid can then be introduced into bacteria, where it replicates as the bacteria grows.[94] Even after a cloned heterologous gene has been introduced into a bacteria and replicated, it is not guaranteed that the gene will be expressed and encode for a protein. E. coli, for example, consists of genetic information for several thousand proteins. Often, a great number of those genes are not expressed at all. Thus, methods that 'turn on' the cloned gene are necessary. Many biotechnological inventions are directed to this field of research.[95]

E. Proteomic research

The determination of the genome changed the entire emphasis of protein studies of the past. It is now possible to comprehend the concrete impact that genetic information has on protein composition and structure. Moreover, it was discovered that different genes neither generate the same amount of proteins nor reveal the precise determination of circumstances under which protein synthesis is initiated. This specification of the total cellular protein output is therefore an important focus of current research efforts.[96]

92 Jollès, Pierre/Jörnvall, Hans, Proteomics in Functional Genomics, Protein Structure Analysis, Basel et al. 2002, XI.

93 Watson, James D., Molecular Biology of the Gene, Menlo Park, California 1987, 208. As for inventions in the field of recombinant technologies see Vossius, Volker/Jaenichen, Hans-Rainer, Zur Patentierung biologischer Erfindungen nach Europäischem Patentübereinkommen und Deutschem Patentgesetz - Formulierung und Auslegung von Patentansprüchen, GRUR 1985, 821, 821.

94 Whitford, David, Proteins: Structure and Function, Chichester, West Sussex, U.K., 315-316.

95 Fernandez, Dennis/Chow, Mary, Intellectual Property Strategy in Bioinformatics and Biochips, Journal of Patent and Trademark Office Society June 2003, 465, 470; Biochip companies, such as Affymetrix and Hyseq, are involved in developing assays, tools, and computational techniques for the disclosure and modification of gene expression profiles; In re O'Farell, 853 F.2d 894, 898.

96 Jollès, Pierre/Jörnvall, Hans, Proteomics in Functional Genomics, Protein Structure Analysis, Basel et al. 2002, XI.

Advances in proteomic science now allow for analyses of known protein forms with regard to their binding regions, the results of which are used for screening against database entries. An important challenge is the need for a simultaneous evaluation of many proteins in highly complex mixtures. Not only must single proteins be identified in order to understand their functional interactions, but also the global output of gene products from essentially all tissues must be determined. This determination has to be carried out under healthy as well as pathogenic conditions, and in developmental and other special states. With the 3-D geometry of proteins being critical to their function, it is important and challenging to preserve this geometry through all research steps. Furthermore, one must take into account that the proteome is constantly changing. One organism will have radically different protein expression in different parts of its body and in different stages of its life cycle.[97]

I. Proteome initiatives

Proteome research is already highly organized on an international level. The "Human Proteome Project" (HPP) has been founded as an analogue to the "Human Genome Project" (HGP).[98] It aims to consolidate national and regional proteome organizations into a worldwide network. Moreover, it engages in scientific and educational activities to encourage the spread of proteomic technologies and to disseminate knowledge pertaining to the human proteome and that of model organisms. Finally, it assists in the coordination of public proteome initiatives. In 2001, the "Human Proteome Organization" (HUPO)[99], again an analogue to the complementary genome initiative, the "Human Genome Organization" (HUGO),[100] was founded.[101] Among other things, its goals are to promote the analysis of particular proteins or protein complexes, as well as their relationship to certain diseases. Moreover, it seeks to advance: the disclosure of biomarker proteins, which allow a diagnosis of disease shortly after its outbreak, the development of diagnostic tools that enable predictions about the course of diseases or its cure, and the disclosure of proteins

97 Jollès, Pierre/Jörnvall, Hans, Proteomics in functional Genomics, Protein Structure Analysis, Functional Genomics, Protein Structure Analysis, Basel et al. 2002, XI.

98 The Human Genome Project started in 1990 and was coordinated by the U.S. Department of Energy (DOE) and the National Institutes of Health (NIH). The project was finished in 2003, when the disclosure of the human genome was completed, see Krefft, Alexander Richard, Patente auf human-genomische Erfindungen: Rechtslage in Deutschland, Europa und den USA, München 2003, 6. For further information see Straus, Joseph, Genpatente: rechtliche, ethische, wissenschafts- und entwicklungspolitische Fragen, Basel, Frankfurt/Main 1997, 16.

99 Human Proteome Organization, available at http://www.hupo.org/, last checked on January 21, 2008.

100 Human Genome Organization, available at http://www.hugo-international.org/, last checked on January 21, 2008.

101 Hanash, Sam, Building a Foundation for the Human Proteome: The Role of the Human Proteome Organization, 3 Journal of Proteome Research 2004, 197.

that can be used as new drugs targets. HUPO encompasses five major initiatives[102], including projects on plasma[103], the liver[104], bioinformatics, and the brain[105]. One of them, the "Human Brain Proteome Project" is carried out under the supervision of the German government. Furthermore, the "Deutsche Gesellschaft für Proteome Forschung e.V." represents the German proteome research in EU, HUPO, and other international proteome organizations.[106] Protein research involves immense investments. The U.S. government, for instance, is supporting a wide range of initiatives in order to cope with challenges in the proteomics field. For example, the National Heart, Lung, and Blood Institute (NHLBI) is supporting 10 proteomic centers with more than U.S. $ 150 million for a period of seven years, and the National Institute of Neurological Disorders and Stroke (NINDS) has detailed plans for other projects.[107]

102 In addition, several sub-initiatives exist, such as for Pan-Asian proteomics, see Mason, Katherine A., As Pan-Asian Proteomics Powerhouse Emerges, Focus is on Liver Cancer, SARS, Genome Technology 2003, 47. All data obtained by the (non-profit) HUPO initiatives are available for public access.

103 Human Plasma Proteome Project, available at http://psidev.sourceforge.net/ppp/pilotPhase/, last checked on September 28, 2005.

104 Human Liver Proteome Project, available at http://www.hlpp.org/hlpp/, last checked on September 28, 2005.

105 Human Brain Proteome Project, available at http://www.hbpp.org/, last checked on January 21, 2008.

106 Deutsche Gesellschaft für Proteome Forschung, available at http://www.dgpf.org/dgpf-set.htm, last checked on January 21, 2005. The Federal Ministry of Education and Research founded the proteomics-based initiative "New efficient procedures for functional proteome analysis" in June 2000. Since then, over 75 million Euro were made available for the development of proteomics-based technologies. For further information see http://www.bmbf.de/en/1756.php, last checked on January 21, 2008. One of the projects that has been sponsored by the ministerial program is "Fighting Mycobacterium tuberculosis with structural proteomics" conducted by the European Molecular Biology Laboratory (EMBL) and several partners (Max-Planck Groups for Molecular Structural Biology, Hamburg; Max-Planck-Institute for Infectious Biology, Berlin; Technical University of Munich, Research Center Weihenstefan, Biomax, Martinsried; Combinature, Berlin; MarResearch, Norderstedt). The project aims to combat tuberculosis under a proteomics approach and has received from the ministry a 3.5 million Euro grant in support of its efforts. For a detailed description, see EMBL Hamburg, MTB-Strukturproteomik Konsortium Gesamtdarstellung, Hamburg, Berlin, München 2003, 1.

107 Lottspeich, Friedrich, Humanproteomorganisation - HUPO, in: Fäden des Lebens, Tagungsband der Münchener Wissenschaftstage im Jubiläumsjahr 2003; München, 2003; 98, 100. The "beat of the proteomic drum" also encouraged many researchers to create private research organizations for the analysis of disease-related proteins, such as the Plasma Proteome Institute, see MacNeil, John S., Like Father, like Son, Genome Technology 2003, 50, 51.

II. Proteomics Technologies

1. Protein expression, purification and characterization

As defined earlier, the major objective of methods employed in proteomics is the total characterization of the protein. A thorough examination of the protein profile requires several steps, ranging from the proteins' identification and structural determination to the study of its post-translational modifications and from its quantification to the handling of the resulting proteomic data. In order to study any protein it is necessary to obtain it in a purified form. This is often a challenging task, particularly if proteins are present within the cell in low concentration. Frequently, this involves the purification of one single protein from a cell paste encompassing over 10.0000 different proteins. Two major alternatives are employed for isolating proteins. First, proteins can be isolated conventionally by obtaining the desired protein directly from the used source, such as a cell or tissue. Second, proteins can be expressed recombinantly, e.g. by introducing the DNA-sequence into a bacterial host.[108] In recent years, there have been numerous technical advances for proteomic technologies. Most commonly used methods for protein separation and identification are 2-D gel electrophoresis for protein separation and the proteome's analysis by mass spectrometry.[109] With the study of some proteins still being difficult to accomplish, further development of these tools is needed.

a) Gel electrophoresis

2D electrophoresis aims to separate proteins according to mass and overall charge. The technology is classified as the most common method for analyzing the purity of an isolated protein.[110] The principle of electrophoresis is the separation of proteins according to molecular mass by their movement through a polyacrylamide gel of closely defined composition under the influence of an electric field. The mobility of a protein through polyacrylamide gels is determined by a combination of overall charge, molecular shape, and molecular weight. The method is conducted by introducing a protein mixture to the top of a gel that proceeds through the matrix because of the electric field, with lighter components migrating faster than 'heavier' molecules. Over time, the component proteins are separated and the resolving power of

108 Whitford, David, Proteins: Structure and Function, Chichester, West Sussex, U.K., 313.

109 Another frequently employed method fort the purification of proteins is chromatography, see Whitford, David, Proteins: Structure and Function, Chichester, West Sussex, U.K., 326. There exist a number of different chromatographic methods.

110 See Gorg, Angelika/Weiss, Walter/Dunn, Michael J., Current two-dimensional electrophoresis technology for proteomics, 4 Proteomics 2004, 3665, 3665. The author considers two-dimensional gel electrophoresis (2-DE) with immobilized pH gradients (IPGs) combined with protein identification by mass spectrometry (MS) 'the workhorse' of proteomics.

the technique is sufficiently high that heterogeneous mixtures of proteins can be separated and distinguished from each other. The movement of proteins through the gel depends on the voltage/current conditions used as well as the temperature. Commonly, the mobility of an unknown protein or mixture of proteins is compared to that of a pure component of known molecular mass. Using this method for individual cell types or organisms makes it possible to identify large numbers of different proteins within proteomes of single-celled organism or individual cells. The technique allows the monomeric molecular mass to be determined with reasonable accuracy. [111]

b) Mass spectrometry

Mass spectrometry has emerged as the central analytical technique in proteomic analysis.[112] Like gel electrophoresis, the method is based on the discovery that the mass of a protein is one of the most useful characteristics for its identification.[113] Its observed parameter is the mass-to- charge ratio of gas phase ions, e.g. of electrically charged proteins in vapor state. Typically, mass spectrometers involve three basic components: an ion source, a mass analyzer and a detector. Ions are produced from samples generating charged states, which the mass analyzer separates according to their charge ratio. Simultaneously, a detector produces quantifiable signals. [114] Finally, the magnitude of these signals is recorded and converted into a mass spectrum. Early mass spectrometers required the sample to be a gas. Modern instrumentation, specifically the popular methods of "matrix assisted laser desorption time of flight (MALDI-TOF)" and "electrospray spectrometry", enable the analysis of ions embedded in a matrix or liquid solution samples. Over the last 20 years mass spectrometry has advanced rapidly and specifically in the area of proteomics. The importance of mass spectrometry for protein characterization was demonstrated by the award of the Nobel Prize for Chemistry in 2002.[115] The introduction of the techniques[116] described above enables accurate mass determination for primary sequences. Moreover, they allow for the detection of post-translational modifications

111 Whitford, David, Proteins: Structure and Function, Chichester, West Sussex, U.K., 333.

112 Recent successes demonstrate the role of mass spectrometry-based proteomics as an decisive tool in molecular and cellular biology, Aebersold, Ruedi/Mann, Matthias, Mass Spectrometry-based Proteomics, 422 Nature 2003, 198, 198.

113 After a protein has been isolated by gel electrophoresis, it is typically analyzed further by mass spectrometry.

114 The development of MALDI-TOF, where a matrix assists in the formation of a gas phase protein ion enabled to overcome existing practical difficulties, such as the non-volatility of proteins.

115 The prize was given to John Fenn and Koichi Tanaka, two pioneers in the field of mass spectrometry, for their research related to the development of 'soft' desorption-ionization methods in mass spectrometry.

116 Such as MALDI-TOF and electrospray methods.

and single residue mutations in genetically engineered proteins. Large numbers of inventions focus on the improvement of mass spectrometry tools. [117]

2. Physical methods of determining the three-dimensional structure of proteins

a) Protein Crystallization

Another core element of proteomics is the development of methods leading to protein structure determination.[118] One of the most common methods of structure determination is protein crystallization. Protein crystals are characterized by a high degree of internal three-dimensional order and a definite overall chemical composition.[119] The crystallization process of molecules of any substance from its solution is characterized by a reversible equilibrium phenomenon, determined by the minimization of the free energy of the system. A solution in which the molecules are fully solvated[120] corresponds to the system at equilibrium; its free energy is minimized. If the amount of molecules in the solution is increased, the system goes through internal changes until the point is reached where there is insufficient liquid to maintain full hydration of the molecules. These conditions are called "the supersaturation state".[121] Crystallizing purified proteins is not only a time consuming process, but also requires a significant amount of protein sample. There are a number of techniques, which have been developed for bringing a protein solution into a supersaturation state. Among them, the most common methods are micro-batch, vapor-

117 Whitford, David, Proteins: Structure and Function, Chichester, West Sussex, U.K., 345. The development of "surface enhanced laser desorption" (SELDI) a technology that facilitates the fast monitoring of biomarkers for cancer diagnosis, is one example of a new mass spectrometry system, see Langbein, William, Mass Spec meets Oncology - A prolific pair of governments researchers developed a Proteomic Bar Code for detecting cancer, Genome Technology 2003, 42, 43. Another recently developed mass spectrometry tool is "Fourier transform mass spectrometry" (FT/MS). It is particularly used for the identification of post-translational modifications; see MacNeil, John S., Making things happen, Genome Technology 2003, 34, 34.

118 Whitford, David, Proteins: Structure and Function, Chichester, West Sussex, U.K., 347.

119 The term crystal comes from the Greek word "krustallos" (clear ice). Like clear ice, crystals are homogeneous solids, many of them having a transparant sparkling appearance and a well-defined geometrical shape, with regular faces and sharp edges, see Chirgadze, Dima, Protein Crystallization in Action, 3, available at http://daffy.bioc.cam.ac.uk/~dima/whitepapers/xtal-in-action/, last checked on July 5, 2005.

120 A liquid substance is considered as solvent if it is capable of dissolving other substances. One characteristic of a solvent is that the substance does not change its state in forming a solution. Solvation is a chemical process in which solvent molecules and molecules or ions of the solute combine to form a compound, see http://www.wordreference.com, last checked on January 21, 2008.

121 See Chirgadze, Dima, Protein Crystallization in Action, 3, available at http://daffy.bioc.cam.ac.uk/ ~dima/whitepapers/xtal-in-action/, last checked on July 5, 2005.

diffusion and dialysis.[122] Although supersaturation of a protein solution can be attained by means of each of these procedures, the underlying principles of these methods differ.

Micro-Batch crystallization[123] involves the direct mixing of the undersaturated protein solution with a precipitant solution. The method aims to produce a final supersaturated concentration, which may eventually lead to crystallization. This is achieved with large amounts of solutions, and typically results in larger crystals owing to the larger volumes of solute present and the lower chance of impurities diffusing onto the face of the crystal. The main disadvantage of the micro-batch technique is that equilibration takes place very rapidly and therefore affects the rate of crystal growth and consequently the quality of the obtained crystals. Nevertheless, since the use of very small volumes of protein solution can be made, the method is quite useful as an early screening method.[124]

Vapor diffusion is the standard method utilized for protein crystallization.[125] It is the favored technique when screening large numbers of conditions.[126] Vapor diffusion is based on evaporation and diffusion of water between solutions of different concentrations as a means of approaching supersaturation of proteins. Typically, the protein solution is mixed in a 1:1 ratio with a solution containing the precipitant agent at the concentration required after vapor equilibration has occurred. A drop is then suspended and sealed over the well solution, which contains the precipitant solution at the target concentration. The difference in precipitant concentration between the drop and the well solution acts as the driving force. It leads to the vaporization of the drop until the concentration of the precipitant in the drop equals that of the well solution.

122 Chirgadze, Dima, Protein Crystallization in Action, 7, available at, http://daffy.bioc.cam.ac.uk/ ~dima/whitepapers/xtal-in-action/, last checked on July 5, 2005; as well as Ng, Joseph D./Gavira, Jose A./Garcia-Ruiz, Juan M., Protein crystallization by capillary counterdiffusion for applied crystallographic structure determination, 142 Journal of Structural Biology 2003, 218 who do not explicitly refer to the method of dialysis.

123 Ng, Joseph D./Gavira, Jose A./Garcia-Ruiz, Juan M., Protein crystallization by capillary counterdiffusion for applied crystallographic structure determination, 142 Journal of Structural Biology 2003, 218, 220. Micro-Batch is a variation of the simple batch crystallization technique.

124 Chirgadze, Dima, Protein Crystallization in Action, 7, available at http://daffy.bioc.cam.ac.uk/ ~dima/whitepapers/xtal-in-action/, last checked on July 5, 2005. This method was successfully conducted in order to obtain the initial NK1 protein crystallization conditions.

125 Ng, Joseph D./Gavira, Jose A./Garcia-Ruiz, Juan M., Protein crystallization by capillary counterdiffusion for applied crystallographic structure determination, 142 Journal of Structural Biology 2003, 218, 220; Whitford, David, Proteins: Structure and Function, Chichester, West Sussex, U.K., 359.

126 Chirgadze, Dima, Protein Crystallization in Action, 10, available at http://daffy.bioc.cam.ac.uk/ ~dima/whitepapers/xtal-in-action/, last checked on July 5, 2005. This technique can also be conducted to increase or decrease the concentration of proteins in the equilibrated state, relative to its initial concentration.

Dialysis techniques are typically conducted for proteins at low and high ionic strength.[127] They employ diffusion and equilibration of small precipitant molecules through a semipermeable membrane as a way of slowly approaching the concentration at which the macromolecule solute crystallizes. In a preliminary step, the protein solution is contained within the dialysis membrane, which is then equilibrated against a precipitant solution. Equilibration against the precipitant in the surrounding solvent slowly reaches supersaturation for the solute within the dialysis membrane, eventually resulting in crystallization. The improvement of dialysis over other methods is in the ease with which the precipitating solution can be varied, simply by shifting the entire dialysis button from one condition to another. Hence, the protein solution can be continuously recycled until the correct conditions for crystallization are obtained.[128]

b) X-ray crystallography

X-ray crystallography is a technique in which the pattern produced by the diffraction of x-rays through the closely spaced lattice of atoms in a crystal is recorded and then analyzed to reveal the nature of that lattice. It can provide an astonishingly fine visualization of protein structure, since it reveals the precise three-dimensional positions of most atoms in a protein molecule.[129]

The material and molecular structure of a substance can often be inferred by quantitative study of this pattern. It is widely used in chemistry and biochemistry to determine the structures of molecules, including DNA and proteins. The first protein structure of myoglobin was disclosed by Max Perutz and Sir John Cowdery Kendrew in 1958 and led to a Nobel Prize in Chemistry.[130] To determine a structure, one must obtain crystals of the protein of interest. This can be a painstaking procedure for macromolecules. Many proteins, such as hydrophobic or membrane-associated proteins, might not crystallize at all. Actually, it is generally possible to achieve crystalline forms of only 5-10 % of proteins, even though increasingly large and complex polypeptides are being crystallized.[131] Some proteins crystallize readi-

127 Whitford, David, Proteins: Structure and Function, Chichester, West Sussex, U.K., 359.

128 Chirgadze, Dima, Protein Crystallization in Action, 10, available at http://daffy.bioc.cam.ac.uk/~dima/whitepapers/xtal-in-action/, last checked on July 5, 2005. Under these conditions, the protein solution can be continiously recycled until the correct conditions for crystallization are obtained.

129 Pusey, Marc L./Liu, Zhi-Jie/Tempel, Wolfram/Praissman, Jeremy/Lin, Dawei/Wang, Bi-Cheng/Gavira, Jose A./Ng, Joseph D., Life in the Fast Lane for Protein Crystallization and X-ray Crystallography, 88 Progress in Biophysics & Molecular Biology 2005, 359 describes X-ray crystallography as the "foremost method" to acquire data relating to the three-dimensional structures for a multitude of proteins.

130 Today, X-ray crystallography is often used to determine how drugs, such as anti-cancer medications, can be improved to better influence their protein targets.

131 See Maggio, Edward T./Ramnarayan, Kal, Recent Developments in Computational Proteomics, 19 Trends in Biotechnology 2001, 266, 266.

ly, whereas others do so only after considerable effort has been spent in determining the optimal conditions. After the crystallization of the substance, the crystals are harvested and often frozen with liquid nitrogen. Freezing the crystals both reduces radiation damage incurred during data collection and decreases thermal motion within the crystal. Crystals are placed on a diffractometer, a machine that emits a beam of x-rays. The x-rays diffract off the electrons in the crystal. The crystal is rotated such that the beam can strike the crystal from many directions. This rotational motion results in an x-ray photograph consisting of a regular array of spots called reflections. The intensity of each spot is measured. These intensities and their positions are the basic experimental data of an x-ray crystallographic analysis. The observed intensities are then used to reconstruct an image of the protein. Furthermore, an electron density map is calculated, which serves for the determination of the density of electrons at a large number of regularly spaced points in the crystal.[132] In the next step, this density map is interpreted. The resolution of the x-ray analysis is determined by the number of scattered intensities. Once a model of a protein's structure has been determined, it is deposited in the Protein Data Bank (PDB).[133] The development of new methods for solving x-ray crystal structures is considered an important field of research.[134]

c) NMR structure determination

Structure Determination of Proteins with NMR Spectroscopy is another classic protein analysis technique. It is accomplished by the determination of the biological macromolecular structure at atomic resolution, but it is only possible with water-soluble proteins. The technique is based on the fact that energy levels of atomic nuclei are split by a magnetic field. Transitions between these energy levels can be achieved by exciting the sample with radiation whose frequency is equivalent to the energy difference between the two levels. The field of NMR spectroscopy has recently experienced an explosive growth, which started with the development of pulsed Fourier-transform NMR and multidimensional NMR spectroscopy and continues today. Progress in the theoretical and practical capabilities of NMR spectroscopy leads to an increasingly efficient utilization of the information content related

132 The term “electron density map” refers to the distribution of electron density in a crystal that is measured by the X-ray diffraction template.

133 Berg, Jeremy M./Tymoczko, John L./Stryer Lubert, Biochemistry, New York, NY, 2002, 110-112. Peters, Linde, http://www.boa-muenchen.org/linde.peters/postgen0.htm#top, Part IV, 1-14.

134 For a method relying on the introduction of iodine into proteins, see Dauter, Zbigniew, Phasing in Iodine for Structure Determination, 22 Nature Biotechnology 2004, 1239.

to it. Parallel developments in the biochemical methods (such as recombinant protein expression) allow simple and rapid preparation of protein samples.[135]

d) Protein modeling (homologous-comparison)

In addition to protein crystallization or synchronization that is not possible with all existing proteins, new computational methodologies have recently yielded modeled structures that are, in many cases, quantitatively comparable to crystal structures.[136] The method of homology modeling of proteins relies on the structural knowledge of proteins for which 3-D structures have been determined, in order to infer the structure of other proteins for which only the sequence is known. The sequence of a polypeptide of unknown structure is combined with the template of another polypeptide in an attempt to predict the unknown structure. Obtained data helps to determine the structure of homologous proteins. For comparative protein modeling, at least one sequence of known 3-D structure with significant similarity to the target sequence is required. Accordingly, protein modeling is only limited by the need for at least one crystal structure within each fold-class to be modeled. In order to determine whether a modeling request can be carried out, one compares the target sequence with a database of sequences derived from a sequence-related protein database using the corresponding bioinformatics program. This method might lead to the selection of several suitable templates for a given target sequence. Commonly, up to ten templates are used in the modeling process. The best template structure, which is the one with the highest sequence similarity to the target, will be chosen as the reference. As a next step, the target sequence needs to be aligned with the template sequence. Residues that are unimportant for the model building will be ignored during the modeling process. Thus, the common core of the target protein and the loops defined by at least one supplied template structure are simulated. Further, the position of each atom in the target sequence is averaged with the help of the location of the corresponding atoms in the template. Those loops for which no structural information is available in the template structure are not defined and thus must be simulated. Most of the known 3-D structures available do not share complete similarity with the template. However, there may be similarities in the loop regions, which can be simulated as loop structure of the new protein. The loop fragments are extracted from the searched protein database. Since each loop is defined by its length and particular atom co-ordinates of its residues, they can be indicated by using particular algo-

135 For a detailed description see Griesinger, Christian, Proteinstruktur-Aufklärung durch 3D-NMR-Spektroskopie, Laborwelt 2003, 10, 10ff; another description is provided by the Max-Planck-Institute for biochemistry, available at: http://www.cryst.bbk.ac.uk/PPS2/projects/schirra/ html/ home.htm, last checked October 12, 2004.

136 Maggio, Edward T./Ramnarayan, Kal, Recent developments in computational proteomics, 19 Trends in Biotechnology 2001, 266-272, providing a general review about computational proteomics.

rithms. Since the templates fail to provide the structural information of many protein side chains, these can therefore not be assimilated in a first attempt and must be added later by further simulation. The amount of side chains required to be constructed depends on the degree of sequence identity between target and template protein. The method has its major weakness regarding protein divergences, which are not connected to any typical homologous family. [137]

III. Data and Bioinformatics for proteomics

1. Databases

To catalogue all human proteins and reveal their function and interaction is an immense challenge for scientists. The number of databases providing biological information is steadily increasing.[138] A new discipline, bioinformatics, has emerged to utilize the information in these databases for a better understanding of biological processes. Bioinformatics scientists work to interpret experimental data. Several sequence and sequence-related databases are available for public use. Additionally, a number of specialized databases exist which focus on a single enzyme, protein family or disease.[139] For amino acid sequences, the databases differ in their content. SWISS-Prot, established in 1986, strives to provide a high level of protein annotation with several cross-links to other databases.[140] Since 2003, it has been carried out by the UniProt Consortium, a collaboration between the Swiss Institute of Bioinformatics (SIB) and the Department of Bioinformatics and Structural Biology of the Geneva University, the European Bioinformatics Institute (EBI) and the Georgetown

137 Maggio, Edward T./Ramnarayan, Kal, Recent Developments in Computational Proteomics, 19 Trends in Biotechnology 2001, 266, 271.

138 Detailed overview of bioinformatics techniques of importance in protein analysis is provided by: Persson, Bengt, Bioinformatics in protein analysis, In: Proteomics in Functional Genomics - Protein Structure Analysis; Jollès, P./Jörnvall, H. Ed. Basel, Boston, Berlin, 2000; 215. Access to most protein databases is free. Recently, however, many providers stopped granting open access and started requiring licenses from commercial users. In the future, even academic users might have to register and pay. Goodman, Phillip, Access Ability, Genome Technology 2004, 21. Carugo, Oliviero/Pongor, Sàndor, The Evolution of Structural Databases, 20 Trends in Biotechnology 2002, 498 emphasize that the evolution of structural databases has been driven by the practical application of structural knowledge.

139 Links to biologically relevant databases are available at the web pages of EBI (European Bioinformatics Institute, Hinxton, England; http://www.ebi.ac.uk), the University of Geneva, Switzerland (http://www.expasy.ch), and NCBI (National Center for Biological Information, Bethesda, MD, USA; http://ncbi.nlm.nih.gov).

140 An annotation gives a narrative description to the formal structure of a protein, Carugo, Oliviero/Pongor, Sàndor, The Evolution of Structural Databases, 20 Trends in Biotechnology 2002, 498, 498.

University Medical Center's Protein Information Resource (PIR).[141] TrEMBL, which stands for Translated EMBL, is another large protein database, carried out by EBI/EMBL[142]. It is constituted in the same format as Swiss-Prot. It consists of computer translations of genetic information contained in the EMBL Nucleotide Sequence Database,[143] which are not yet integrated in SWISS-PROT. PIR (Protein Information Resource),[144]a U.S. protein related organization, has established the Protein Sequence Database (PSD) that contains functionally annotated protein sequences, which grew out of the "Atlas of Protein Sequence and Structure" (1965-1978) edited by Margaret Dayhoff. [145]Apart from that, GenPept is a database, which contains translated protein-coding sequences, which were produced by translating open reading frames from GenBank, the NIH genetic sequence database.[146] Furthermore, 3-D structures of biological macromolecules are collected in the Protein Data Bank (PDB) maintained by the Research Collaboratory for Structural Bioinformatics (RCSB).[147] More recently, another data resource has been initiated in In-

141 Available at http://www.expasy.org/sprot/sprot_details.html, last checked on January 21, 2008.

142 The European Molecular Biology Laboratory is a non-profit organization and a basic research institute funded by public research monies from 20 member states. Research at EMBL is carried out by approximately 80 independent groups covering the whole spectrum of molecular biology. The Laboratory is divided into five units: the main Laboratory in Heidelberg, and Outstations in Hinxton (the European Bioinformatics Institute), Grenoble, Hamburg, and Monterotondo in the Rome region. The key issues of EMBL's work are: to perform basic research in molecular biology, to train scientists, students and visitors at all levels, to provide crucial services to scientists in the member states, and to develop new instruments and methods in the life sciences, and technology transfer. The European Bioinformatics Institute (EBI) is associated with EMBL.
See http://www.embl-heidelberg.de/aboutus/index.html, last checked on January 20, 2008.

143 The EMBL Nucleotide Sequence Database (also referred to as EMBL-Bank) is Europe's primary nucleotide sequence collection. The DNA and RNA sequences are mainly obtained from submissions of individual researchers, genome sequencing projects, and patent applications. The database is maintained in an international collaboration with GenBank (USA) and the DNA Database of Japan (DDBJ), available at http://www.ebi.ac.uk/embl/, last checked on January 21, 2008.

144 Further information on the Protein Information Resource center is available at: http://pir.georgetown.edu/, last checked on January 21, 2008.

145 Dayhoff, M. O., Eck, R. V. and Park, C. M. Atlas of Protein Sequence and Structure, Vol. 5, 75, London 1979, published by National Biomedical Research Foundation (NBRF).

146 GenBank contains a collection of all publicly available DNA sequences, which are released at the NCBI ftp site, available at ftp://ftp.ncbi.nih.gov/genbank/gbrel.txt, last checked on January 21, 2008. Open Reading Frames (ORFs) are DNA protein-coding sequences, which devoid of stop codons and are therefore suitable for RNA polymerase, see Alberts, Bruce/Johnson, Alexander.Lewis, Julian, Molecular Biology of the Cell (4th ed.), New York 2002, 110-111.

147 Available at http://www.pdb.bnl.gov.; the PDB is common ancestor of all structural databases. It was established in 1971. Over the years, the quantity, phenotype and quality of the deposited structures have changed due to new experimental techniques. A good description is provided by Carugo, Oliviero/Pongor, Sàndor, The Evolution of Structural Databases, 20 Trends in Biotechnology 2002, 498, 499.

dia, where the "Institute of Bioinformatics" (founded in 2002) works to establish the "Human Protein Reference Database" (HPRD)[148] – "a centralized platform to visually depict and integrate information pertaining to domain architecture, post-translational modifications, interaction networks, and disease association for each protein in the human proteome." Most of the protein annotation data it contains is more or less redundant with SWISS-Prot; the interaction data, however, goes far beyond. It is set apart by manual curation, which means a reliable way to control quality compared to other databases that are created by automatic processes. So far, none of the existing databases can be considered an established standard, in fact all are still in their early stages. Hence, the existing variety offers scientists the possibility of choosing instead of imposing one database by default. The latest accomplishment of a 'Human Proteome Atlas for Normal and Disease Tissue, established by the Swedish Human Proteome Resource (HPR) program, funded by the Knut and Alice Wallenberg Foundation, however, represents a highlight of proteomics endeavor that might set new standards for proteomic research.[149]

2. Cross-linking of database information

In 2000, the Swiss Institute of Bioinformatics (SIB) and the European Bioinformatics Institute (EBI) founded the Human Proteomic Initiative (HPI) with the major goal to annotate, describe and distribute a large amount of information concerning human protein sequences to the life science community. Being aware of the huge complexity of the proteome, the initiative aims to annotate all known human sequences according to the quality standards of SWISS-Prot. These standards include more than 9000 annotated human sequences associated with about 23200 literature references; 22600 experimental or predicted PTM's, 2800 splice variants and 15100 polymorphisms. The interpretation of all known human sequences for each known protein includes a wealth of information. It refers to the description of its function, domain structure, subcellular location, post-translational modifications, and variants or similarities to other proteins. The HPI project contains a number of subcomponents, such as

- Analysis of all known human proteins,
- analysis of mammalian orthologs[150] of human proteins,
- analysis of all known human polymorphisms at the amino acid level,

148 Genome Technology 10, 2003, 16.

149 The protein atlas aims to demonstrate the expression and localization of proteins in large variety of normal tissue and cancer cells. The basic concept of the resource centre is to produce antibodies to human target proteins. The antibodies are subsequently used for functional analysis of the corresponding proteins in numerous further platforms.
See http://proteinatlas.org/, last checked on January 21, 2008.

150 Proteins orthologs are proteins that have evolved from the same inherited region.

- analysis of all known post-translational modifications in human proteins,
- tight links to structural information, and the
- classification of all known vertebrate proteins.[151]

3. Database screening and drug design

The structure-based screening approach aims to identify a subset of an existing or a virtual library of compounds with an enhanced probability of binding. Typically, the first step of drug development is the selection of an adequate target. When a high-quality structure is available for investigation, it can be used to screen databases or libraries of existing chemical substances. The screening process will then select those substances containing an array of chemical groups compatible with binding to the targeted binding pocket of the protein.

Compounds possessing the desired binding characteristics are analyzed in further tests. If the tested effect is confirmed, it is examined to determine whether the compound is pharmaceutically acceptable and toxicologically safe. If the drug succeeds, auxiliary substances are added for the final stage of the pharmaceutical process.[152] Drug development research using 3-D structure information can be illustrated using the graphical description depicted in figure 8.[153]

151 The web-page of HPI is available at http://www.expasy.org/sprot/hpi/hpi_desc.html, last checked on January 21, 2008.

152 Maggio, Edward T./Ramnarayan, Kal, Recent Developments in Computational Proteomics, 19 Trends in Biotechnology 2001, 266, 271. The process of drug discovery involves immense labors. For views from inside the pharmaceutical industry, see Mervis, Jeffrey, The Hunt for a New Drug: Five Views from the Inside, 309 Science 2005, 722, 722.

153 The figure was adopted from Masuoka, Kunihisa, Study on the Ways of Protection of Post-Genome Research Products, IIP Bulletin 2002, 84, 87.

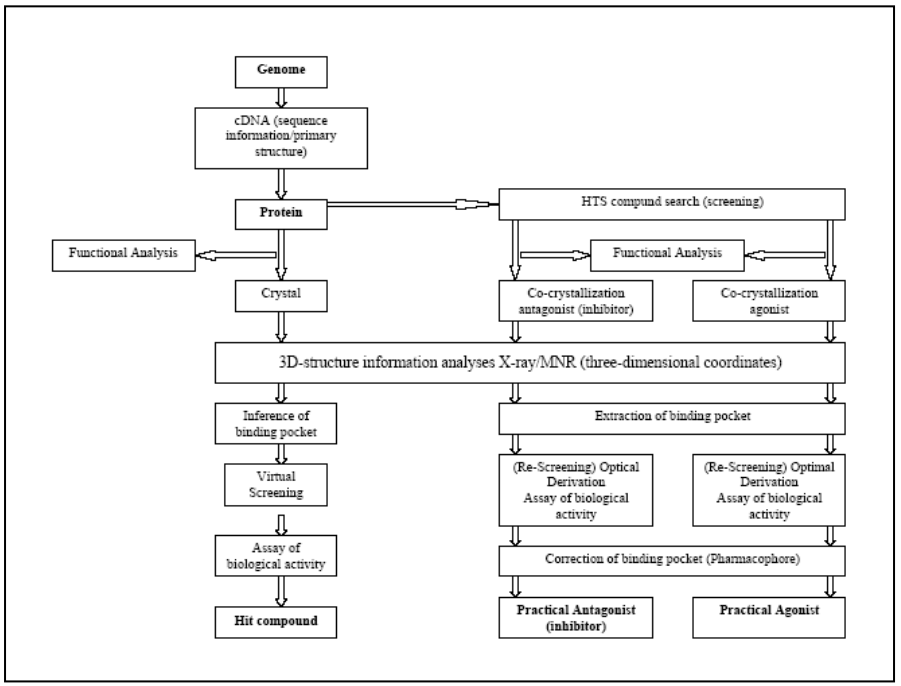

Figure 8: Stylized illustration of proteomic drug design

4. In-silico screening of binding pockets

In-silico[154] screening methods are methods that aim to scan chemical/ pharmaceutical compounds for new drug design. They involve the computerized simulation of the three-dimensional structure of a polypeptide. The simulated protein is then used to screen several pharmaceutical compound-related databases. In order to determine the pharmaceutical/chemical response of binding pocket properties the screening methods comprise several steps. These include the application of 3-D molecular modeling algorithm to the atomic coordinates of a protein, the determination of the spatial coordinates of binding pockets, and the electronic screening of candidate compounds against the spatial coordinates of the protein. The major goal is to identify compounds that can bind to the computerized protein. More precisely, the molecular model simulates the positions of heteroatoms in the amino acids, which form the binding pockets of the protein. It also includes information about hydrogen

154 From literally: 'in the computer'.

bonds. The coordinate data of the computerized protein is then incorporated in the database such that the interatomic distances between the atoms of the simulated protein is retrieved. In a further step, the distances between the bonding of different candidate compounds and the atoms that bind in the computerized protein model are compared. Thereby, it is possible to identify those candidate compounds that would theoretically form the most stable complex with computerized 3-D model.[155] The obtained ligands can efficiently be used for the development of new drugs.[156]

In-silico screening methods replace the traditionally used *in vitro*[157] methods, which were generally based on a 'trial and error' approach. The Human Genome Project and the improvement of protein analysis techniques has lead to a dramatic increase in the information to be interpreted. The method of in vitro research thus became too expensive and time consuming. However, since an *in-silico* screening is only hypothetical and based on simulated structures, it always requires *in vitro* testing of useful identified compounds in order to verify that the underlying technical problem of finding an appropriate agent has indeed been solved. Consequently, a biological evaluation of the obtained compounds is necessary.[158]

155 A good overview is provided by Gnanakaran, S./Nymeyer, Hugh/Portman, John/ Sanbonmatsu, Kevin Y./Garcia, Angel E., Peptide Folding Simulations, 13 Current Opinion in Structural Biology 2003, 168.

156 See note: Innovatives in-silico Verfahren beschleunigt Wirkstoffsuche, Transkript 2004, 28, emphasizing that most recent in-silico methods rely upon protein structure homology for the search of new compounds.

157 In an artificial environment outside a living organism or body, for example, testing conducted in the laboratory.

158 Lonati, Milena, Patentability of Receptors and Screening Methods: Does in silico Screening Pose New Legal Problems? Bioscience Law Report 2000/2001, 144, 145.

Chapter 3: Patentability Requirements

A. Statutory Background and Fundamental Case Law in Europe and the U.S.

I. Introduction

As outlined in chapter II above, the tertiary structure is the single most important determinant of a protein's biological function.[159] Research related to drug design that is conducted on grounds of the tertiary folding type has a more reliable basis than studies that solely involve the knowledge of primary structures. The goal of this chapter is to provide an overview of the legal terrain faced by those seeking to patent protein 3-D structure related claims. The requirements of the patentability of proteomic claims depend on statutory background on the one hand and existing case law related to chemical, biotechnology and software inventions on the other. Thus, as a first step, the applicable law will be presented regarding the patentable subject matter, industrial application/utility, specification/written description, enablement and novelty and/or inventive step.

Next, the major case law will be examined. Cases related to biotechnological material will be used to exemplify how patent law systems have coped with the new genomic technologies. Since proteins are considered chemical compounds, the legal treatment of molecular structures will also be reviewed. One particular focus will be the patenting of primary structure-related protein inventions, where problems have mainly occurred regarding the novelty and inventive step requirement. Patent examiners have resolved these issues by applying certain principles, which will be developed in detail below. Such a comprehensive description will form the basis of subsequent chapters, which discuss the applicability of traditional patent law standards to 3-D, or proteomic, structures.

II. Applicable law in the U.S. and Europe

In order to be granted a patent in compliance with American patent law, at least the following criteria must be met: subject matter eligibility and utility (35 U.S.C. § 101), written description (35 U.S.C. § 112 1), enablement (35 U.S.C. § 112 1), clarity (35 U.S.C. § 112 2) novelty, no loss of rights (35 U.S.C. § 102), and non-obviousness (35 U.S.C. § 103). European patents are granted for any invention that is susceptible to industrial application, is new and involves an inventive step (Art. 52 I EPC). According to the practice of the EPO, an invention as understood in patent

159 See at Chapter 1 B II 2.

law is a "practical teaching, which requires the claimed subject-matter or activity to have a technical character, and which is capable of being realized and repeatable and provides a solution to a problem based on technical consideration."[160]

1. Patentable Subject Matter

a) U.S.

The fundamental principle of U.S. patent law is that one may patent that which is new. According to § 101, a patentable subject matter is determined as "any useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof".[161] As for the patenting of genes or proteins in the human organism, the intuitively appealing objection is that they themselves are not new. The human genome and the encoded proteins have existed in humans apart from any inventive effort of anyone who might seek to patent them.[162] The reasoning in *Funk Brothers Seed Co. v. Kalo Inoculant Co.* in 1948 was based on this argument.[163] The Supreme Court found the patent claims that were directed to a mixed culture of different strains of bacteria invalid and argued that patents cannot be issued for the discovery of a phenomenon of nature

> "The qualities of these bacteria, like the heat of the sun, electricity, or the qualities of metals, are part of the storehouse of knowledge of all men. They are manifestations of law of nature, free to all men and reversed exclusively to none."[164]

In light of a broad reading of *Funk Brothers*, DNA sequences and human proteins could not be considered as patentable subject matters. Although the *Funk Brother* decision never has been officially overruled, subsequent patent law does not deny the patentability of all inventions consisting of naturally occurring products or laws of nature. In the 1980 decision of *Diamond v. Chakrabarty*[165], the Supreme Court again touched the question of patentability of biotechnological inventions. The patent claim referred to living microorganisms into which the inventor had introduced multiple naturally occurring plasmids. These rings of bacterial DNA encompassed genetic information that resulted in the organism's ability to break down multiple components of crude oil. The USPTO found the plasmids not to be "products of nature", since bacteria containing the introduced plasmids did not occur in nature. Nevertheless, it rejected the claims on the ground that living organisms as such

160 Schulte/Moufang, PatG mit EPÜ, § 1, No. 19.
161 Chisum, Donald/Nard, Craig Allen/Schwartz, Herbert F./Newman, Pauline/Kieff, F. Scott, Principles of Patent Law, New York 2001, Chapter 3.
162 Eisenberg, Rebecca, Patenting the Human Genome, 39 Emory Law Journal 1990, 721, 723.
163 Funk Brothers Seed Co. V. Kalo Inoculat Co., 333 U.S. 127 (1948).
164 Funk Brothers Seed Co. V. Kalo Inoculat Co., 333 U.S. 127, 130.
165 Diamond v. Chakrabarty, 447 U.S. 303 (1980).

would not be patentable subject matter.[166] The Supreme Court concluded that a living, genetically modified organism may be patentable as a new "manufacture" or "composition of matter" under section 101. The Court distinguished *Funk Brothers* on the grounds set forth as follows: while the patent holder in *Funk Brothers* had not modified the function of any of the species of root-nodule bacteria in the mixed-culture inoculant, Chakrabarty had formed "a new bacterium with markedly different characteristics from any found in nature". The discovery thus was "not nature's handiwork, but his own; accordingly it is patentable subject matter …." In order to support this wide range of the categories of patentable subject matter, the Court relied on the language from committee reports accompanying the 1952 Patent Act, to the effect that Congress intended statutory subject matter to "include anything under the sun that is made by man." The question of distinguishing patentable subject matter and products of nature depends on whether the claimed invention is the result of human invention. With regard to human DNA sequences, one might still reason that they should not be patentable as such, although they might be a patentable subject matter in the creation of recombinant material that incorporates human genes. Nevertheless, a substantial amount of case law concludes that newly isolated or purified materials may be patented even though those materials exist in nature in an impure state. As long as the purified material offers some advantages, it is sufficient that a patent applicant has made the sequences available in an isolated or purified form that does not exist in nature.[167] In *Merck & Co. v. Olin Mathieson Chemical Corp.,* a patent was granted on purified vitamin B12 isolated from fermentation materials. The Court upheld the validity of the patent, arguing that the patent product was advantageous to the previously available vitamin B12 from cattle due to its relatively abundant supply, cheap price, freedom from toxic substances, and amenability to control potency and dosage. As a whole, the Courts' reasoning suggested that there should be no bar to patenting a "product of nature" assuming the invention is new, useful, falls within the categories of patentable subject matter under section 101, and complies with all further statutory patent requirements.[168]

In sum, *Diamond v. Chakrabarty* opened the door for the patenting of biological material. It thus can be considered as a decisive step in the rise of the biotechnological industry. Its economic implications have indeed been much further reaching than those of the German *Red Dove* decision, which will be discussed next.[169]

166 Eisenberg, Rebecca, Patenting the Human Genome, Emory Law Journal, 39 Emory Law Journal 1990, 721, 725.

167 Eisenberg, Rebecca, Patenting the Human Genome, 39 Emory Law Journal 1990, 721, 726-727.

168 Merck & Co. V. Olin Mathieson Chemical Corp. 253 F.2d 156 (4th Cir. 1958).

169 Straus, Joseph, Biotechnology and Patents, 54 Chimia 2000, 293, 293.

b) Europe

aa) Patentability of biological material

In Europe, for many decades, inventions involving biological material were not considered patentable on grounds that they were not 'technical' but 'a product of nature'. This approach has been radically changed by the landmark decision of *Red Dove*[170], where the patent application was directed to a method for breeding a dove with red plumage.[171] The German Federal Supreme Court clearly extended the field of technology so as to cover biological phenomena and forces, defining them as

> "… [a] teaching to methodically utilize controllable natural forces to achieve a causal, perceivable result, …, provided that teaching meets the general prerequisites of industrial application, novelty, [etc.]."[172]

The court reasoned that there generally are three possibilities of biological inventions that have been considered patentable in theory and practice:

> -If the course of biological events is affected with means other than animate matter;
>
> - if inanimate matter is influenced by biological means and
>
> - if the means as well as the final result lie within the field of biology.

The patent application at issue belonged to the third category of possibilities in which a biological result is obtained either solely by or primarily as the result of biological means. Thus, patentability would in principal be possible. Nevertheless, it was necessary that the method of breeding be recurrent. Lacking such requirement, a patent could not be granted. Although a patent was not granted for the claim at issue, the decision clearly approved the patentability of biological inventions as eligible subject matters. [173]

With the goal of providing high and harmonized standards of protection for biotechnology comparable to those in the U.S. and Japan, the European Commission adopted the Directive on the Legal protection of Biotechnology Inventions (98/44/EC) ('the Directive') in 1998.[174] The Directive, which became effective on

170 BGH, 1 IIC 136 (1970) - Red Dove (Rote Taube); see also Herrlinger, Karolina A., Die Patentierung von Krankheitsgenen: dargestellt am Beispiel der Patentierung der Brustkrebsgene BRCA 1 und BRCA 2, München 2005, 115.

171 Straus, Joseph, Biotechnology and Patents, 54 Chimia 2000, 293, 293; the "Red Dove case" also is the starting point for the modern jurisdiction on the patentablility of biological inventions in Germany, Straus, Joseph, Patenting Human Genes in Europe - Past Developments and Prospects for the Future, 26 IIC 920, 920 (1995); Benkart/Melullis, EPÜ, Art. 53, No. 44.

172 BGH 1 IIC 136, 137 (1970) - Red Dove (Rote Taube); see also Busse/Keukenschrijver, PatG, § 1, No. 24.

173 BGH 1 IIC, 137ff (1970) - Red Dove (Rote Taube).

174 Benkard/Schäfers, PatG, § 34 No. 37e; Jaenichen, Hans-Rainer/Mcdonell, Leslie A./Haley, James F., Jr., From Clones to Claims, Cologne, Berlin, Bonn, Munich 2002, 2; Straus, Joseph, Biotechnology and Patents, 54 Chimia 2000, 293, 295.

July 6, 1998, strikes a balance between the commercial needs of scientists and industry and the ethical concerns of some of the public that strongly opposed the idea of patenting living material.[175] The contracting states of the EU were supposed to put the Directive into practice within two years of the date of publication by changing the national practice and law where necessary. Irrespectively, the process of implementation in each of the member states took much longer than expected. After three years, only four member states, United Kingdom, Finland, Denmark and Ireland, had actually put the rule into practice. The European Court of Justice rejected an action of annulment against the Directive that was filed by the Netherlands and supported by Italy and Norway.[176] In 2004, Germany was convicted by the European Court of Justice for having failed to implement the Directive into national law. Consequently, the German legislature reacted and implemented the Directive in February 2005 by amending the German Patent Act.[177]

With the EPO not being linked to the European Union, the Directive does not have any direct influence on the EPC.[178] However, in order to harmonize the EPO's practice with the EU Directive, the Implementing Regulations to the EPC were amended by a decision of the Administrative Council of the European Patent Organization on June 16, 1999. For this amendment, the EPO introduced several new rules. On December 13, 2007, a revised version of these rules entered into force.[179] To incorporate the Directive into the EPC, the EPO introduced Rule 26 (former 23b) (General and definitions), Rule 27 (former 23c) (Patentable biotechnological inven-

175 As for the concerns of the different groups of interest in Germany, see particularly 'Entwurf eines Gesetzes zur Umsetzung der Richtlinie über den rechtlichen Schutz biotechnologischer Erfindungen', Bundestagsdrucksache 14/5642 (November 23, 2001), 1-24 (reasons and statements provided by the German Federal Council and the German Federal Government; see also Straus, Joseph, Biotechnology and Patents, 54 Chimia 2000, 293, 295.

176 EuGH C-377/98 in: GRUR Int 01, 1043 = BIPMZ 01, 357 Biotechnology Directive; see also Schulte/Moufang, PatG mit EPÜ, § 1 No. 79. According to the French view, the patenting of human genes is violating human dignity. Consequently, France rejected the implemenation of the rule into its national law and asked the Commission to reconsider the Directive. In a statement that strongly supported this policy, the French National Committee on Ethics in the Life and Health Sciences summarized the underlying considerations. For example, it stated: "L'exigence qui porte à exclure cette connaissance du gène de la brevetabilité rejoint deux autres préoccupations éthiques le souci de maintenir le corps humain, ses éléments et ses produits hors des circuits marchands, l'apparition d'une aspiration au partage des bienfaits attendus de la connaissance du genome," Comité Consultatif National d'Ethique pour les sciences de la vie et de la santé, "Avis sur l'avant-projet de loi portant transposition, dans le code de la propriété intellectuelle de la directive 98/44/CE du Parlement européen et du Conseil, en date du 6 juillet 1998, relative à la protection juridique des inventions biotechnologiques," 8 Juin 2000, para 6), available at http://www.ccne-ethique.fr/francais/start.htm, last checked on December 10, 2006.

177 The details of the European Court of Justice's verdict and of the German Patent Act amendment will be discussed in Chapter IV D below.

178 Benkard/Melullis, EPÜ, Art. 53, No. 39; Straus, Joseph, Biotechnology and Patents, 54 Chimia 2000, 293, 295.

179 Decision of the Administrative Council, Act revising the European Patent Convention of 29 November 2000.

tions), Rule 28 (former 23d) (Exceptions to patentability) and Rule 29 (former 23e) (The human body and its elements).[180] Rule 26(1), second sentence (former 23 b (1)) establishes the general principle that the Directive "shall be used as a supplementary means of interpretation" of the EPC.[181] The basic principles of the Directive are listed in Recitals 35-46. These include the exclusion from patentability for processes for treatment of the human or animal body by surgery or therapy and diagnostic methods (Recital 35) and the guarantee of *ordre public* or morality (Recitals 37 and 39). The Directive also contains a commitment to the special importance of the "ethical clause", where it is indicated that all ethical aspects of biotechnology must be interpreted in light of the specified principles of patent law and specifically evaluated by the Commission's European Group on Ethics in Science and new Technologies (Recital 44).[182] With regard to biological material, the Directive confirms the practices that were approved in the German *Red Dove* decision by introducing the patentability of biological material or processes.[183] The principle applies also to biological material, provided it is isolated from the natural environment or produced by means of a technical process (Art. 2(1)(a)(Rule 23b (3) EPC; Art. 3(1) (2); Rule 27(a) EPC (former Rule 23c (a)).[184]

bb) Exclusions from patentability

The approach to what constitutes patentable subject matter can be considered a major difference between the European and the U.S. patent law system. As illustrated in *Diamond v. Chakrabarty*, the U.S. Patent Act does not contain any specific exclusions or exceptions from patentability.[185] Rather, the courts are responsible for setting the limits inherent in the principles of the patent system. In contrast, European patent law is characterized by several of such exclusions and exceptions and many are specifically directed to the field of biotechnology.[186]

Section 52 EPC excludes certain matters from patentability. Items on this list include, in particular, discoveries, scientific theories, mathematical methods, aesthetic

180 Jaenichen, Hans-Rainer/Mcdonell, Leslie A./Haley, James F., Jr., From Clones to Claims, Cologne, Berlin, Bonn, Munich 2002, 3.

181 Schulte/Moufang, PatG mit EPÜ, § 1, No. 6, citing Rule 23b(1) Second Sentence; see also Straus, Joseph, Biotechnology and Patents, 54 Chimia 2000, 293, 295.

182 For the "ethical dimension of the patent law system" as expressed in Art. 53(a) EPC see Moufang, Rainer, Patentierung menschlicher Gene, Zellen, und Körperteile? - Zur ethischen Dimension des Patentrechts, GRUR 1993, 439, 442. Despite Art. 53(a) EPC the European Patent Office issued large numbers of gene patents without raising any ethical issues; Straus, Joseph, Patenting Human Genes in Europe - Past Developments and Prospects for the Future, 26 IIC 920, 926 (1995).

183 Schulte/Moufang, PatG mit EPÜ, § 1 No. 86.

184 Straus, Joseph, Biotechnology and Patents, 54 Chimia 2000, 293, 295.

185 Diamond v. Chakrabarty, 447 U.S. 303 (1980), see Chapter 3 A II 1 a).

186 Schulte/Moufang, PatG mit EPÜ, § 1 Nos. 86ff, see also Straus, Joseph, Biotechnology and Patents, 54 Chimia 2000, 293, 294.

creations, schemes, rules and methods for performing mental acts, playing games or doing business, programs for computers and presentations of information.[187] Lacking a technical character, a discovery does not provide a practical teaching and is therefore not patentable. [188] This is particularly relevant for inventions involving biotechnological substances. Under the foregoing definition, the revealing of a previously unrecognized substance occurring in nature is a mere discovery. If the patent applicant, however, shows in which way the substance was isolated from its natural environment or how a technical process had produced it, patentability is established. Thus, the mere description of biological material is not sufficient. If a repeated success in isolating a biological substance, like a protein or a gene, is not guaranteed, the invention does not establish a technical teaching and lacks patentability.[189] The disclosed technical teaching, i.e. the isolation of the biological substance, must be repeatable.[190]

The House of Lords' decision in the case of *Asahi Kasei Kogyo's Application* can be considered decisive for determining the threshold for genetic sequences disclosures.[191] Here, the application in suit [the 'Asahi-Application'] disclosed and claimed a physiologically active polypeptide produced by genetic engineering and useful in treating human tumors. The Asahi-Application was rejected by the Patent Office on the grounds that they lacked novelty in view of a co-pending application. The co-pending application was filed after the priority date of the application in suit but claimed priority from an earlier application, which disclosed and claimed the polypeptide but failed to explain how to obtain and how to use the genetic sequences coding for it. The applicant appealed to the English House of Lords asserting that the co-pending application was not an effective anticipation because the only document of earlier priority did not contain an enabling disclosure.[192] The House of Lords concluded that, for anticipation "published information is required to contain an enabling disclosure." An invention is "not made available to the public merely by a published statement of its existence, unless the method of working is so self-evident as to require no explanation."[193] As for the description of the polypeptide,

187 Guidelines for Examination in the EPO, Part C-IV, § 2, available at http://www.epo.org/patents/law/legal-texts/guidelines.html, last checked on January 21, 2008. The list established in Art. 52 EPC is not complete, but is seen to provide a number of examples, see Busse/Keukenschrijver, PatG, § 1, No. 39.

188 Singer/Stauder, EPC, Vol 1, Art. 52, No. 24.

189 Schulte/Moufang, PatG mit EPÜ, § 1 No. 93. A patent applicant establishes patentability for natural substances if he provides "the discovery of a technical application of the discovery." The patent is granted, because the substance was "previously not available." Therefore, the public is not being denied access to something previously accessible; see Singer/Stauder, EPC, Vol 1, Art. 52, No. 25.

190 Schulte/Moufang, PatG mit EPÜ, § 1 No. 98.

191 Asahi Kasei Kogyo's Application, [1991] R.P.C. 485 (House of Lords). See also Cornish, William/Llewelyn, David, Intellectual Property: Patents, Copyright, Trade Marks and Allied Rights, 6th ed., London 2007, 190.

192 Asahi Kasei Kogyo's Application, [19 91], R.P.C. 485, 486.

193 Asahi Kasei Kogyo's Application, [1991], R.P.C. 485, 486.

the court stated "[f]or a chemical product (as what the polypeptide was treated) the invention does not consist in the formula itself, but in a description of a method", because a person skilled in the art will need to know "a method by which it can be produced."[194] In light of these principles, the co-pending application did not destroy the novelty of the Asahi-application, since it failed to provide any methods for preparing the claimed polypeptide.[195]

Further, Directive 98/44/EC implements the principle of non-commercialization of the human body. Art. 5(1) states that "[t]he human body, at various stages of its formation and development, and the simple discovery of one of its elements, including the sequence or partial sequence of a gene" are excluded from patentability. The Implementing Regulations to the EPC, Rule 29 EPC (former 23e (1) EPC) follows this standard.[196] However, an element isolated from the human body or otherwise produced in the course of a technical process, which is industrially applicable, may be eligible as a patentable subject matter, even if the structure of that element is identical to that of a natural element. As set forth above, biological material that is isolated from its natural environment or produced in the course of a technical process may be patentable.[197] Non-isolated genes in their natural environment, by contrast, are considered mere discoveries.[198]

With regard to computerized methods of protein analysis, the exclusion of computer programs plays an important role. The question will be addressed in the course of the following case study. At this point, it has already been stressed that exclusions are only made if the listed subject matters are claimed "*as such*".[199] The former version of Art. 52(4) EPC stated that methods for treatment of the human or animal body by surgery or therapy and diagnostic methods practiced on the human or animal body are not susceptible to industrial application and therefore excluded from patentability.[200] The exclusion does not apply to certain products, e.g., pharmaceuticals, which are considered industrially applicable even if used for medical treatment.[201] In light of the fact that the provision was found to be systematically incor-

194 Asahi Kasei Kogyo's Application, [1991], R.P.C. 485, 486.

195 See Tumour Necrosis Factor, 2 IIC 247 (1993), particularly the comment by Rainer Moufang in the same issue who notes that in the light of the House of Lords' decision, a patent application referring to biological material anticipates later filed applications if others "under no obligation of confidentiality had access to the said material at the critical date," at 258.

196 Ahrens, Claus, Genpatente - Rechte auf Leben? Dogmatische Aspekte der Patentierbarkeit von Erbgut, GRUR 2003, 89, 91.

197 Guidelines for Substantive Examination, Part C-IV, § 2a.2 available at http://www.epo.org/patents/law/legal-texts/guidelines.html, last checked on January 21, 2008

198 Krefft, Alexander Richard, Patente auf human-genomische Erfindungen: Rechtslage in Deutschland, Europa und den USA, München 2003, 266.

199 As for the difficulties that exist with the interpretation of the term "as such", see Busse/Keukenschrijver, PatG, § 1, No. 41.

200 Busse/Keukenschrijver, PatG, § 5, No. 19.

201 Methods which are employed outside the human body (ex vivo), on a blood or other sample also do not fall under the definition of diagnostic methods practised on the human body,

rect - since methods are excluded on public interest grounds and not due to the lack of industrial patentability[202] - the 2000 revision of the EPC, put into force on December 13, 2007, cancelled the rule. What used to be the rule under Art. 52(4) EPC is now added as c) under Art. 53 EPC:

> "European patents shall not be granted in respect of: c) methods for treatment of the human or animal body by surgery or therapy and diagnostic methods practiced on the human or animal body; this provision shall not apply to products, in particular substances or compositions, for use in any of these methods."

2. Utility and Industrial Applicability

a) U.S. (Utility)

Two statutory provisions establish the framework for analyzing the utility requirement. As recited in 35 U.S.C. § 101:

> "Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title."

The second provision with regard to the utility requirement is 35 U.S.C. § 112. It is related to the disclosure the patent applicant is obliged to make. Section 112, first paragraph explicitly requires a patent specification to disclose "the manner and process of making and using [the invention]." The concrete meaning of these two phrases has largely been developed by the courts. As for chemical research, chemical scientists often develop a chemical substance without a particular purpose in mind. Often, chemical compounds are synthesized which are believed to be useful some day for something, but for which no particular use is currently known. As for biotechnology, scientists may isolate interesting genes or gene fragments whose use is not known or completely analyzed. Sometimes researchers are able to understand that genes are triggered in many diseased cells, even though the protein that the gene is encoding is yet unknown.[203]

In 1999, the office issued the Revised Utility Guidelines, as clarification of the final Utility Examination Guidelines as published in 1995.[204] These guidelines can be considered a direct reaction to public comments expressing doubts regarding the pa-

Bostyn, Sven J.R., Enabling Biotechnological Inventions in Europe and the United States: A Study of the Patentability of Proteins and DNA Sequences with Special Emphasis on the Disclosure Requirement, Munich 2001, 115.

202 EPO, Special Edition No. 4, OJ 2007, 48.

203 Merges, Robert Patrick/Duffy, John Fitzgerald, Patent Law and Policy: Cases and Materials, Newark, San Francisco, Charlottesville 2002, 229.

204 1999 Revised Utility Guidelines, 64 Fed. Reg., 71440 (Dec. 21, 1999), which were published in response to comments regarding the earlier Guidelines, published at 60 Fed. Reg. 36263 (1995).

tentability of ESTs. In particular, the PTO determined that it had received comments that the 1995 Utility Guidelines would permit the patenting of ESTs "when the sole disclosed use of an EST is to identify other nucleic acids whose utility was not known, and the function of the corresponding gene is not known."[205] The 1999 Revised Utility Guidelines also account for allegations that "PTO examination procedures would result in granting patents based on non-specific and non-substantial utilities, contrary to established case law."[206] Consequently, the 1999 Guidelines determine that a "claimed invention must have a specific and substantial utility."[207] The guidelines did not amend the rules of the 1995 Utility guidelines with regard to other aspects, such as "credibility" and "well-established" utility.

In 2001, the USPTO again issued a new version of its guidelines on utility.[208] The 2001 Utility Guidelines provide a substantial amendment of the 1995 version. Particularly, the guidelines require that utility is only created, if the utility of a patent application is "specific", "substantial", and "credible".[209] Furthermore, the 2001 Utility Guidelines determine that - if it becomes apparent that an invention bears a "well-established utility" - the claim should not be rejected due to a lack of utility. A "well-established" utility is assumed if (a) a person skilled in the art would easily be able to determine why an invention is useful due to the properties of an invention, and (b) the utility is specific, substantial, and credible.[210] As for a specific and substantial utility, the USPTO indicates that "throw-away", "insubstantial", and "non-specific" utilities, such as the use of a complex invention as landfill are excluded. With regard to credibility, the guidelines held that "[c]redibility is assessed from the perspective of one of ordinary skilled in the art in view of the disclosure and any other evidence of record (e.g. test data, affidavits or declarations from experts in the art, patents or printed publications) that is probative of the applicant's assertions."[211]

Thus, one must distinguish between applications defining an invention's specific use and those indicating an ambiguous or unsubstantiated potential use. A general statement that a compound has "useful biological" properties and might aid in the treatment of some unnamed disorders is too vague to qualify as a specific utility. A "substantial utility" should establish a "real world" use. If a "real world" context for using the invention is not reasonably apparent from the record, then the asserted utility is not substantial.[212] It is inappropriate to label certain types of inventions as incapable of having a specific and substantial utility based solely on the setting in which the invention is used, for example, inventions used in a research or laboratory setting. Many research tools used in laboratory analysis and the assessment of com-

205 1999 Revised Utility Guidelines, 64 Fed. Reg. 71440, 71441.
206 1999 Revised Utility Guidelines, 64 Fed. Reg. 71440, 71441.
207 1999 Revised Utility Guidelines, 64 Fed. Reg. 71440, 71441.
208 2001 Utility Guidelines, 66 Fed. Reg. 1092. (Jan. 5, 2001).
209 2001 Utility Guidelines, 66 Fed. Reg. 1092, 1098.
210 2001 Utility Guidelines, 66 Fed. Reg.1092, 1098.
211 2001 Utility Guidelines, 66 Fed. Reg. 1092, 1098.
212 Merges, Robert Patrick/Duffy, John Fitzgerald, Patent Law and Policy: Cases and Materials, Newark, San Francisco, Charlottesville 2002, 249.

pounds, such as gas chromatographs, screening assays, and nucleotide sequencing techniques, have a clear, specific, and substantial utility in a research or intermediate context. However, this evaluation alone does not focus on the invention's overall utility in a patent sense. Instead, it is necessary to distinguish between inventions identifying a current and specific substantial utility and those requiring additional or future research to establish or verify usefulness. In this process, applicants' use of labels such as "research tool", "intermediate," or "for research purposes" are not determinative of whether the claimed invention has a specific, substantial and credible utility.[213]

A number of cases illustrate how patent examiners and courts struggle with setting the exact threshold for the utility requirement. In *Brenner v. Manson*[214]*,* the inventor applied for a patent on an allegedly novel process for making certain known steroids. A patent examiner denied the application, and the denial was affirmed by the Board. The ground for rejection was the failure "to disclose any utility for the chemical compound produced by the process".[215] The failure was not cured, according to the Patent Office, by the inventors reference to an scientific article revealing that steroids of a class, which included the compound in question, were undergoing screening for tumor-inhibiting effects in mice, and that a homologue adjacent to this steroid had proven effective in that role. The U.S. Supreme Court reconfirmed that one may patent only that which is "useful". The reference to the article, however, could not create utility, since the "presumption that adjacent homologues have the same utility has been challenged in the steroid field because of a greater known unpredictability of compounds in that field".[216] The court clearly stated that where the sole "utility" consists in its potential role as an object of use-testing, a practical or specific utility does not exist. A patent should be "no award for the search, but a compensation for its successful conclusion".[217]

In *In re Brana,* the applicants filed a patent application directed to compounds for use in combination with anti-tumor substances that were based on a specific chemical formula.[218] The specification stated that the given substitutions produce compounds with "better action and a better action spectrum than anti-tumor substances" established in a particular reference.[219] The reference described a computer-assisted evaluation of specific chemicals which had been screened for anti-tumor activity by testing their efficacy *in vivo*. Further, in comparing the effectiveness of the claimed compounds with structurally similar compounds, the applicants' patent specification disclosed the cytoxicity of the claimed compounds against human tumor cells, *in*

213 Kunin, Stephen G/Nagumo, Mark/Stanton, Brina/Therkorn, Linda S./Walsh, Stephen, Reach-through Claims in the Age of Biotechnology, 51 American University Law Review April 2002, 609, 623.
214 Brenner v. Manson, 383 U.S. 519 (1966).
215 Brenner v. Manson, 383 U.S. 519, 521
216 Brenner v. Manson, 383 U.S. 519, 532.
217 Brenner v. Manson, 383 U.S. 519, 536.
218 In re Brana, 51 F.3d 1560 (Fed. Cir. 1995).
219 In re Brana, 51 F.3d 1560, 1562.

vitro, and held the opinion that these tests "had a good action".[220] The Court of Appeals for the Federal Circuit concluded that the applicant's disclosure complied with the requirements of 35 U.S.C. Section 112 (1). According to the court, the disclosed tumor models represent a specific disease against which the claimed compounds are alleged to be effective. In light of the given references, the applicant's specification alleges a sufficiently specific use. Even if one skilled in the art would be convinced of the applicant's asserted utility "… applicants proffered sufficient evidence to convince one of skill in the art of the asserted utility."[221] The provided test results showed that several compounds within the scope of the claims exhibited significant anti-tumor activity and thus would have been sufficient to satisfy applicants' burden.[222]

The early Supreme Court reasoning of *Brenner* gained particular importance in the light of the patenting of cDNA sequences. Craig Venter, a scientist working at the National Institutes of Health (NIH), initiated a project involving the documentation of all cDNA sequences matching the mRNA for each gene in the active, protein-encoding DNA sequences in a human brain. The c in cDNA refers to "complementary". A complementary DNA sequence is defined as the sequence matching the "genetic messenger" carrying the encoded information for a particular gene, the messenger RNA or mRNA.[223] Since only the exons of a DNA strand are translated into protein, the RNA only consists of the complementary information of the exons themselves. The cDNA thus must be considered as the complement of the translated exons and consequently is distinguishable from the original DNA. Before Venter initiated his work, libraries of cDNA fragments had been documented, but no one had obtained detailed base pair sequences for each fragment. Venter had only to sequence a portion of the cDNA segments, and with that portion the gene sequence itself, the actual gene, could be identified or reconstructed. He named the partial sequences "expressed sequence tags" or "ESTs". In a patent application, he claimed each of the ESTs he had produced. The U.S. National Institutes of Health (NIH) requested a legal opinion on the validity of the patent application. The opinion denied validity, reasoning in light of *Brenner*:

> "Use of the ESTs as probes to obtain full cDNA sequences has no practical benefit unless and until the full sequences themselves may be used for some purpose beyond research. Subsequent research may well prove some of the genes useful for diagnosis or therapeutic purposes, but the information disclosed in the specification fails to identify which of the genes will be useful, or for which purposes. Practical utility of the sequences awaits determination of the function of the genes they are associated with …"[224]

220 In re Brana, 51 F.3d 1560, 1563.
221 In re Brana, 51 F.3d 1560, 1567.
222 In re Brana, 51 F.3d 1560, 1567.
223 Merges, Robert Patrick/Duffy, John Fitzgerald, Patent Law and Policy: Cases and Materials, Newark, San Francisco, Charlottesville 2002, 250.
224 Eisenberg S. Rebecca; Merges,/Merges, Robert P., Opinion Letter as to the Patentability of Certain Inventions Associated with the Identification of Partial cDNA Sequences, 23 American Intellectual Property Law Association Q. J. 1995, 16-19.

Based on the opinion, Venter's patent application was ultimately dropped by NIH after having created a storm of controversy.[225] The demonstrated case law was finally summarized in the U.S. utility guidelines, which had been issued in 1995 in response to criticism of pervasive utility rejections involving biotechnology and therapeutic method claims.[226]

In *In re Fisher,* the patent applicant attempted to claim five ESTs that coded for parts of certain proteins in maize plants.[227] At the time Fisher filed the patent application, he "did not know the precise structure or function of either the genes or the proteins encoded for by those genes". The application encompassed seven uses of the claimed ESTs in an attempt to satisfy the utility requirement. The Federal Circuit concluded that "none of Fisher's seven asserted uses meets the utility requirement of § 101."[228] The court clearly determined that an "application must show that an invention is useful to the public as disclosed in its current form, not that it may prove useful at some future date after further research," and "must disclose a use which is not so vague as to be meaningless."[229] EST's coding parts of proteins with unknown function were seen as merely "objects upon which scientific research could be performed with no assurance that anything useful will be discovered in the end."[230] The court found that Fisher had not actually used gene fragments for any of the listed uses in the real world.[231] Consequently, Fisher's invention lacks "substantial" utility.[232] Fisher's patent application also does not have a "specific" utility, because "[a]ny EST transcribed from any gene in the maize genome has the potential to perform any one of the alleged uses." Therefore, "nothing about Fisher's seven alleged uses" makes the five claimed ESTs different from "any EST derived from any organism."[233]

b) Europe (Industrial Applicability)

According to Art. 57 EPC, a patent must be susceptible to industrial application, which means that it can be made or used in any type of industry, including agriculture. In compliance with the guidelines of the EPO, "industry" is construed in its

225 Merges, Robert Patrick/Duffy, John Fitzgerald, Patent Law and Policy: Cases and Materials, Newark, San Francisco, Charlottesville 2002, 253, Straus, Joseph, Patenting Human Genes in Europe - Past Developments and Prospects for the Future, 26 IIC 920, 934 (1995).
226 USPTO, Utility Examination Guidelines, 60 Fed. Reg. 36, 263 (1995).
227 In re Fisher, 421 F.3d. 1365, 1372 (Fed. Cir. 2005).
228 In re Fisher, 421 F.3d. 1365, 1370.
229 In re Fisher, 421 F.3d. 1365, I371.
230 In re Fisher, 421 F.3d. 1365, 1373.
231 In re Fisher, 421 F.3d 1365, 1374.
232 In re Fisher, 421 F.3d 1365, 1374.
233 The court emphasized that "[t]he claimed ESTs themselves are not an end of Fisher's research effort, but only tools to be used along the way in the search for a practical utility." In re Fisher, 421 F.3d 1365, 1374.

broad sense as including any physical activity of "technical character", and a useful or practical art rather than an aesthetic art.[234] The guidelines provide a list of industrially applicable inventions. Generally, they state that an invention not corresponding to the listed inventions will not be considered industrially applicable.[235] The Implementing Regulations to the EPC have incorporated the EU-Directive and require that the industrial application must be disclosed in patent applications for partial sequences of genes, Rule 29 (former Rule 23e(3)).

The European patent system reacted also to the development that large numbers of ESTs and Single Nucleotide Polymorphisms (SNPS) in the U.S. were filed for patentability.[236] The 'Biotechnology Directive' set forth in Recital 23 that a mere DNA sequence without the indication of a given function does not provide any technical information and therefore lacks industrial applicability. "Function" in this context must be understood as any function causing a technically applicable result, such as use as a diagnostic marker or screening tool. In the cases in which a sequence or partial sequence is used to produce a protein or part of a protein, the industrial applicability is only established if the patent application indicates which protein or part of a protein is produced or what function it serves (Recital 24). The EPO adopted this requirement in the Implementing Regulations to the EPC, Rules 26-29 EPC (former Rules 23b-23e EPC) and the case law of the Opposition Division approved the new established principles. In *Novel V28 seven transmembrane receptor,*[237] the division had to examine whether the requirement of industrial application was satisfied. The patentee argued that pursuant to Art. 57 EPC the requirement of industrial application of an invention is satisfied "if it can be made or used in any kind of industry". Thus, he alleged that the disclosure of how to make and to use a protein would be sufficient. The Opposition Division disagreed, maintaining that such disclosure does not provide a credible function of a DNA sequence encoding a protein and thus rejected the patent based on a lack of industrial application. With regard to the application of the Biotechnology Directive, the division stated:

> "The requirements of industrial application of biotechnology inventions are set by Rules 23b-23e EPC which concern European patent application and patents. Thus, the provisions of said rule apply to the present procedure and the recitals of European Directive 98/44/EC are applicable as supplementary means of interpretation. In view of the requirement of industrial application as set in Art. 57 in conjunction with Rule 23b-e EPC, the invention cannot be acknowl-

234 Industrially requires that the invention as such can be manufactured industrially or used in any sort of industrial field, see Busse/Keukenschrijver, PatG, § 5, No. 8.

235 Guidelines for Examination in the EPO, Part C-IV, 4, available at http://www.epo.org/patents/law/legal-texts/guidelines.html, last checked on January 21, 2008.

236 The European, Japanese and United States Patent Offices conducted a Trilateral study on the patenting of EST (Trilateral Project B3b on "The Patentability of DNA Fragments). For an analysis of their approaches see, Howlett, Melanie J./Christie, Andrew F., An analysis of the approach of the European, Japanese and United States Patent office to Patenting Partial DNA Sequences (ESTs), 34 IIC 581 (2003).

237 Decision of the Opposition Division of June 21, 2001, V28 receptor/Icos, OJ 2002, 293-308.

edged as industrially applicable because industrial applications are not disclosed in the patent application (Rule 23e(3)EPC)."[238]

3. Novelty

In the case of proteomic inventions, a major question which emerges is whether the three dimensional structure is sufficient to fulfill the novelty requirement. For such a classification, patent law principles related to the field of chemistry are of particular interest, because chemistry provides a comparable field of research. Stereochemistry is referred to as the study of the three-dimensional shape of molecules.[239] With regard to patent law, the novelty of diastereomers and enantiomers[240]is a frequently discussed issue.[241] The precise details will be demonstrated in the course of the proteomic-related case study below. At this point, the general statutory background as to novelty will be illustrated. To illustrate the entire legal terrain which proteomic inventions must face, the principles applicable to biochemistry and particularly classical protein research are also presented.

a) U.S.

Under 35 U.S.C. § 101, an invention must be "new."[242] In compliance with Section 102(a), it lacks novelty if it is "known or used by others" in the United States, or "patented or described in a printed publication" in the US or a foreign country.[243]

238 Decision of the Opposition Division of June 21, 2001, V28 receptor/Icos, OJ 2002, 293-308, 303.

239 For an introduction into the field of stereochemistry, see Alworth, William L., John Wiley & Sons, Inc., Stereochemistry and Its Application to Biochemistry, New York 1972.

240 Isomers are compounds bearing the same atomic compositions, but different physical and/or chemical properties. Stereoisomers are isomers consisting of atoms that differ only by their orientation in space. Diasteromers are stereoisomers that are non-superimposable, but are not mirror images. Enantiomers are stereoisomers that are non-superimposable mirror images. See IUPAC Compendium of Chemical Terminology, available at http://www.iupac.org/publications/compendium/index.html, last checked on January 21, 2008.

241 See particularly T12/81 Diastereomere, OJ 1982, 296; T990/96, N. Publ.(EPO 1998); T296/87 Enantionmers/Hoechst, OJ 1990, 195; T1048/92, N. Publ.(EPO 1994); T600/95, N. Publ.(EPO 1996); T1048/92, N. Publ.(EPO 1994). As for the U.S. patent law practice, see In re Doyle, 293 F.3d 1355 (Fed. Cir. 2002), also Domeij, Bengt, Pharmaceutical Patents in Europe, Stockholm 2000, 146.

242 For a brief summary on the novelty requirement, see also Rader/Adelman, Cases and Materials on Patent Law, 248-249.

243 As explained by Chisum, the meaning of the novelty requirement is further determined in Section 102(e) which „bars a patent on an invention described in a patent application published under Section 122(b) or a patent by another filed in the United States before the invention thereof by the applicant for patent. In addition, "Section 102(g) bars a patent on an in-

The distinction between the different paragraphs of 35 U.S.C. § 102 requires careful examination. Subsection (f) can be interpreted as the requirement that the patent applicant has actually invented the subject matter. It is prohibited to derive or steal it from others. Furthermore, the provision covers two major aspects: the novelty requirement as such and statutory bar subsections. Both requirements refer to timing issues. The novelty subsections are directed only to events that take part prior to the time of invention:

> § 102 (a): "before the invention thereof by the applicant", (e) (same expression), and (g): "before such person's inventions thereof".

In contrast, the statutory bar subsections may be matched by events occurring after the invention. For instance, § 102(b) prohibits the granting of a patent if the invented subject matter was disclosed in a printed publication more than one year prior to filing for a patent. Likewise, subsections (c) and (d) are also triggered by events (abandonment, foreign filing by the applicant) that takes place after the applicant's invention.[244]

In sum, novelty requires the inventor to comply with subsections (a), (e) and (g). The inventor's right to obtain a patent, however, will be lost if any event matches up with one of the statutory bars found in subsections (b) – (d). Therefore, the statutory bars are called "loss of right to patent". It is thus important to note that the U.S. defines novelty according to the date of invention. In contrast, Europe measures novelty as of the filing date.[245] The requirement that all elements of the claimed invention must be identically described in a single prior art reference ("All Elements Rule"), however, is valid in Europe as well as in the U.S. Accordingly, anticipation requires that every feature of the claimed invention must be taught - explicitly, implicitly or by incorporation by reference - in a single piece of prior art.[246] There are no specific guidelines regarding the novelty examination practice of the USPTO.

As for biological products, the "All Elements" rule often results in the question of how a given prior reference is distinguishable from a slightly modified recombinant form. In *Scripps Clinic & Research Foundation v. Genentech, Inc.*,[247] the defendant held that the alleged invention related to a recombinant product was anticipated by a published dissertation and three declarations by its author. The cited dissertation, however, differed from the "fingerprint" identification of the invention (a VIII:C

vention that before [a person's] invention therof ... was made in this country by another inventor who had not abandoned, suppressed, or concealed it."[citation omitted], see Chisum, Donald, Chisum on Patents, Volume 1, § 3.01.

244 Merges, Robert Patrick/Duffy, John Fitzgerald, Patent Law and Policy: Cases and Materials, Newark, San Francisco, Charlottesville 2002, 363.

245 Merges, Robert Patrick/Duffy, John Fitzgerald, Patent Law and Policy: Cases and Materials, Newark, San Francisco, Charlottesville 2002, 363.

246 Scripps Clinic & Research Found. v. Genentech, Inc. 927 F.2 d 1565, 1576 (Fed. Cir. 1991); Amgen, Inc. v. Hoechst Marion Roussel, Inc., 126 F.Supp. 2d 69, 91 (D.Ma.2001) Put simply, anticipation requires that every element of the claimed invention be previously described in a single reference.

247 Scripps Clinic & Research Found. v. Genentech, Inc. 927 F.2d 1565.

Factor) obtained by the patentee. The Court of Appeals for the Federal Circuit concluded that the given prior art reference did not establish anticipation, in that it did not identically demonstrate each element of the claimed invention. Accordingly, the Court remanded the case for trial to determine whether there were differences between the "fingerprint" factor (human factor VIII:C) derived from plasma and that produced by recombinant technology, such as purity, specific activities, stability, and formulations.[248]

Anticipation will be avoided if a claimed composition is of increased purity, in contrast to its unpurified appearance occurring in nature. In *In re Bergstrom* the invention was related to two chemical compounds (PGE(2) and PGE(3)).[249] The claims at issue were rejected due to the lack of novelty. The USPTO stated that the specification gave references indicating that the claimed compounds naturally occurred in natural glandular material, or in a variety of fractions and liquors derived from the glandular material. The Court concluded that novelty existed, finding that the claimed compounds exhibited a higher purity than those occurring in nature and stated that "[p]ure materials necessarily differ from less pure or impure materials and, if the latter are the only ones existing and available as a standard of reference, as seems to be the situation here, perforce the 'pure' materials are 'new' with respect to them."[250] The court, however, emphasized that

> "[w]hether the claimed pure materials have the same usefulness or assortment of properties as the impure materials of the prior art … is a question having no bearing on the factual and legal matter whether pure materials are new vis-à-vis impure materials within the meaning of § 101, although it is but one of the factors to be considered in determining their obviousness under 35 U.S.C. § 103."[251]

Accordingly, the court did not examine whether the purer compound is sufficiently different to constitute a "new and useful … manufacture, or composition of the matter, as required in 35 U.S.C. § 101"[252] Section 101 is rather equated with the standard of novelty under § 101 and a more pure compound is considered to meet the

248 Scripps Clinic & Research Found. v. Genentech, Inc. 927 F.2d 1565, 1576-1578, (Fed. Cir. 1991). A number of further Federal Circuit decisions affirm that a prior art publication must be enabling in order to anticipate an invention, see Chisum, Donald, Chisum on Patents, Volume 1, § 3.04 [1][b][iii], FN 19, citing, for instance, Transclean Corp. v. Bridgewood Services, Inc. 290 F.3d 1364, 1362 (Fed. Cir. 2002); Bristol-Myers Squbb Co. v. Ben Venue Laboratories, Inc. 246 F.3d 1368, 1374 (Fed. Cir. 2002).

249 In re Bergstrom , 427 F. 2d 1394 (C.C.P.A. 1970).

250 In re Bergstrom , 427 F. 2d 1394, 1402.

251 In re Bergstrom , 427 F. 2d 1394, 1402.

252 The approach to the purity problem taken by the Court of Customs and Patent Appeals was fundamentally different than the approach taken in earlier cases. In, for instance, Parke-Davis & Co. v. H.K. Mulford & Co. (1911), 189 F.95 (S.D.N.Y. 1911), aff'd 196 F.496, (2d. Cir. 1912), a compound was considered as new only if it differs "in kind" from the old compound. Such a difference "in kind" will normally be found only if the new pure compound has an entirely new utility from the old one. See also Merck & Co. v. Olin Mathieson Chem. Corp., 253 F.2d 156, 164 (4th Cir. 1958), Chisum, Donald, Chisum on Patents, Volume 1, § 1.02[9].

standard of novelty under § 102(a). Patentability of the compound, however, is decided under the question of non-obviousness.[253]

The question of purity is treated differently with regard to the patenting of a metabolite of a new drug. In *Schering Corp. v. Geneva Pharmaceuticals, Inc.*[254], the patent claimed a metabolite of a known drug (loratadine). The prior art disclosed this drug teaching that it could be administered to a human subject. It did not, however, disclose the later-patented metabolite. The Federal Circuit found that the claim to the metabolite was invalid, because of anticipation by inherency. The court, however, stated that a "proper" claim to the metabolite in synthetic or purified form would have had established novelty. The court explained that "[a] skilled patent drafter … might fashion a claim to cover the metabolite in a way that avoids anticipation. For example, the metabolite may be claimed in its pure and isolated form."[255]

Pursuant to Section 102(g), a patent is anticipated if "before the applicant's invention thereof the invention was made in this country by another who had not abandoned, suppressed, or concealed it." This provision is of a particular interest when parallel research is carried out by competing teams of invention entities.[256] In *Amgen, Inc. v. Chugai Pharmaceutical Co.*,[257] the claim to a purified and isolated DNA sequence expressing human erythropoietin was questioned to be anticipated by the previous work of others who had initially developed a probing strategy. Without the probing method, the isolation of the gene would not have been possible. However, the knowledge of the specific amino acid sequence of erythropoietin was necessary for isolating the gene. At the time the alleged prior invention was made, the specific amino acid sequence was still unknown. The Federal Circuit concluded that the prior disclosed probing method itself did not defeat novelty, because it did not disclose how to obtain the "purified and isolated DNA sequence". The court determined that for an "adequate conception" of the invention, the inventor must be able to "describe his invention with particularity." This requires both "(1) the idea of the invention's structure and (2) possession of an operative method of making it"[258] In contrast to the earlier invention, the claim at issue to the specific DNA probes provided all ne-

253 See, for instance, Ex Parte Gray, 10 USPQ2d 1922, 1927 (Bd. Pat. App. & Int'f 1989).
The approach taken to the issue of "more pure compounds" in earlier cases continues the standard applied by the courts in more recent cases, see, for instance, Glaxo Group Ltd. v. Apotex, Inc., 376 F.3d.1339 at 1349 (Fed. Cir. 2004) (Patents claiming antibiotic drug and method of preparing such drug were not anticipated by prior art patent, despite testimony of expert that he was able to use prior art patent to create claimed formulation, in view of expert's admitted deviation from relevant example of prior art patent and his reading of one patent at issue prior to conducting his experiments.).

254 Schering Corp. v. Geneva Pharmaceuticals, Inc., 339 F.3d 1373 (Fed. Cir. 2003).

255 Schering Corp. v. Geneva Pharmaceuticals, Inc., 339 F.3d 1373, 1381.

256 Chisum, Donald, Chisum on Patents, Volume 1, § 3.05[4].

257 Amgen, Inc. v. Chugai Pharmaceutical Co. 927 F. 2d 1200 (Fed. Cir. 1991), cert. denied, 112 S. Ct. 169 (1991).

258 Amgen, Inc. v. Chugai Pharmaceutical Co. 927 F. 2d 1200, 1206.

cessary information. Therefore, the court concluded that novelty was not destroyed under § 102(g) by the prior invention of the other researchers.[259]

Similarly, the questioned claim of *Fiers v. Sugano*[260] was directed to "a DNA which consists essentially of a DNA which codes for a human fibroblast interferon-beta polypeptide."[261] The court reasoned that the DNA could be obtained by the knowledge of its specific nucleotide sequence. The mere knowledge of how to prepare the DNA would not serve as a conception of the compound. The court stressed that anticipation "does not occur unless one has a mental picture of the structure of the chemical, or is able to define it by its method of preparation, its physical or chemical properties, or whatever characteristics sufficiently distinguish it".[262] Accordingly, a mere determination of the DNA by its principal biological property was not sufficient. In contrast, "a precise definition, such as by structure, formula, chemical name, or physical properties" would be necessary in order to provide sufficient identification.[263]

b) Europe

Pursuant to Art. 54(a) EPC "an invention shall be considered to be new if it does not form part of the state of the art". The state of the art, for the purpose of considering novelty, comprises "everything made available to the public by means of written or oral description, by use, or in any other way, before the date of the filing of the European patent application" (Art. 54(2) EPC).[264] In addition, "the content of European

259 Amgen, Inc. v. Chugai Pharmaceutical Co. 927 F. 2d 1200, 1205-1207. The rule that another inventor must have had an "adequate conception" of a new technology for anticipation was confirmed by Invitrogen Corp. v. Clonetech Laboratories, 429 F.3d 1052 (Fed. Cir. 2005) ("competitor did not show by clear and convincing evidence that researcher conceived of genetically engineered reverse transcriptase enzyme with no RNase H activity, but having DNA polymerase activity, before critical date"). The prior inventor must be diligent in reducing the invention to practice, see Monsanto Comp. v. Myogen Plant Science, 261 F.3d 1356, 1370 (Fed. Cir. 2001) ("The evidence is sufficient … to support presumed jury findings that Agracetus was diligent throughout the entire critical period in creating and testing the modified Bt genes")

260 Fiers v. Sugano, 984 F.2d 1164 (Fed. Cir. 1993).

261 Fiers v. Sugano, 984 F.2d 1164, 1166.

262 Fiers v. Sugano, 984 F.2d 1164, 1168.

263 Fiers v. Sugano , 984 F.2d 1164, 1171. A patent interference is an administrative proceeding pursuant to 35 U.S.C. §§ 102(g) and 135(a). During such a proceeding the Board is authorized to determine not only priority of invention but also to redetermine patentability. 35 U.S.C. § 6(b), see Capon v. Eshhar, 418 F.3d 1349, 1351, 1358 (Fed. Cir. 2005) (the Federal Circuit during interference examined the written description requirement, stating that an invention must not be "fully presented," if the claimed subject matter is known).

264 A detailed description of what belongs to the state of the art is provided by the EPO decision EBA1/92, Availability to the public, OJ 1993, 277-280. (The Enlarged Board of Appeals held that "the chemical composition of a product is state of the art when the product as such is available to the public and can be analysed and reproduced by the skilled person, irrespec-

patent applications as filed, of which the dates of filing are prior to the date referred to in paragraph 2 and which were published under Art. 93 on or after that date shall be comprised in the state of the art" (Art. 54(3) EPC. Thus, the EPC distinguishes between a real and a fictitious state of the art.[265] The real state of the art comprises all knowledge made available to the public by means of written or oral description, other means such as video recording, sound recording, or the Internet.[266] In order to preclude double patenting, the fictitious state of the art includes prior not disclosed patent applications, given that they have been published on or after the date of the more recent application (Art. 93 EPC) and that they are still effective, e.g. have not been withdrawn or otherwise become invalid.[267] Hence, inventions that are already subject of another European patent are not patentable.[268]

The Examination guidelines of the EPO instruct examiners to classify an invention as novel provided that it differs from what is known in the prior art.[269] Examiners consider prior art documents as of the effective date of the document. It is not permissible to combine separate items of prior art together, each document must be compared in isolation.[270] This differs from what is considered in the context of the inventive step requirement. Pursuant to Article 56 EPC "an invention shall be considered as involving an inventive step if, having regard to the state of the art, it is not obvious to a person skilled in the art." Thus, not the single document but the whole prior art is considered.[271] Art. 54(2) EPC states that the relevant date for the determination of the state of the art is the filing date of the European Patent application. Pursuant to Art. 89 EPC, the date of filing can be replaced by the date of priority.[272] Unlike American patent law, European law requires absolute novelty (Art. 54(1) EPC).

With regard to 3-D protein structures, a crucial question is whether the description of the tertiary structure is sufficient to establish novelty in cases in which the primary structure has already been disclosed. To answer this question, the case law

tive of whether or not particular reasons can be identified for analyzing the composition"). Id. at 280. See also Cornish, William/Llewelyn, David, Intellectual Property: Patents, Copyright, Trade Marks and Allied Rights, 6th ed., London 2007, 181-82.

265 Benkard/Melullis, EPÜ, Art. 54 Nos. 202-203.

266 Benkard/Melullis, EPÜ, Art. 54, Nos. 33-51.

267 Benkard/Melullis, EPÜ, Art. 54 No. 203; Straus, Joseph, Neuheit, ältere Anmeldungen und unschädliche Offenbarungen im europäischen und deutschen Patentrecht, GRUR Int. 1994, 89, 94.

268 Benkard/Melullis, EPÜ, Art. 54 No. 5. Prior PCT applications for which the EPO acts as the designated Office have the same effect if they have been translated into one of the official languages and the national fee has been paid, Art. 150(3) in conjunction with Art. 150(1), Art. 158(2) EPC, Singer/Stauder/Spangenberg, EPC – Vol. 1, No. 87.

269 Guidelines for Examination in the EPO, Part C-IV, 7.1.

270 Guidelines for Examination in the EPO, Part C-IV, 7.1.

271 For mosaic consideration of prior art and the question of enablement, not merely the single document but all documents in combination are relevant, see Guidelines for Examination in the EPO, Part C-IV, 9.8.

272 Singer/Stauder/Spangenberg, EPC, Vol. 1, Art. 54, No. 12; Rogge, Rüdiger, The concept of Novelty with Particular Regard to Conflicting Patent Applications, 28 IIC, 794 (1997).

related to classical protein research will be considered. In classical protein research (mostly related to the analysis of primary structure), a patent to a protein invention was considered to be novel pursuant to the following rules.[273] The disclosure of the complete amino acid sequence destroyed the novelty of a protein. The majority of protein inventions, however, cannot be classified that easily. In some, the biological activity of a protein is known without any knowledge of the enzymatic complex causing that activity. In others, some characteristics of the enzyme-substrate complex are disclosed, e.g. through determination of certain physical and chemical parameters of a partial purified protein. The question then is to determine whether the disclosure of an amino acid sequence, which was previously not known, is still sufficient to establish novelty. For a classification of the above-mentioned cases, certain rules are applicable. The first principle is one of a series of principles developed by the German Federal Supreme Court regarding the characterization of macromolecular substances through process parameters. In *Trioxane,*[274] the court stated that a description of a substance is only sufficient if it clearly identifies and distinguishes the substance from others. Accordingly, the information provided by prior art is only novelty destroying if it is sufficient for clear identification. The same standard is applied by the EPO. In *T51/95 Mature leukocyte interferons/Hoffmann-La-Roche*[275] novelty was acknowledged, since the claimed interferon molecule had not been unambiguously characterized in the prior art. Thus, the patent – covering a human bacterial-produced leukocyte interferon – was granted.[276]

aa) The principle of unambiguous parameters

The application of a new parameter for the identification of a substance already clearly identified by a previously established parameter does not create novelty. Consequently, the disclosure of new characteristics of the same substance, e.g. the disclosure of the formula, biological activity or certain physical effect will not create novelty in such a case.[277] If, however, a previously established parameter does not provide sufficient information for the clear identification of a substance, the disclo-

273 A detailed overview of the EPO's decisions on novelty for protein inventions is provided by Jaenichen, Hans-Rainer/Mcdonell, Leslie A./Haley, James F., Jr., From Clones to Claims, Cologne, Berlin, Bonn, Munich 2002, 257-267.

274 BGH, 3 IIC 226 (1972) - Trioxane.

275 T51/95 Mature leukocyte interferons/Hoffmann-La-Roche, N. Publ.

276 T51/95 Mature leukocyte interferons/Hoffmann-La-Roche, N. Publ., No. of the Reasons 19-24; see also T 71/95 Immunoassay/Amersham International plc, N. Publ., No. of the Reasons 8 (for finding lack of novelty a direct and unambiguous disclosure in the prior art is necessary).

277 Benkard/Melullis, EPÜ, Art. 54, No. 176. A new parameter, however, is sufficient for the description of a substance that differs from the already disclosed substance, if it clearly indicates on what the difference is based, see Schulte/Moufang, PatG mit EPÜ, § 1, No. 348.

sure of further properties may still establish novelty.[278] For instance, if only the biological activity of the protein is known in the prior art, the first isolation of the carrier responsible for such activity is enough for establishing novelty. Even though the biological activity of a protein may be considered substantial information about such protein, it cannot be considered a sufficient parameter for its identification.[279] In the case that all disclosed parameters can be combined and therefore establish sufficient and unambiguous substance identification, the disclosure of any further parameter does not create novelty.[280] Due to the high number of similarities between different protein groups, many parameters, however, cannot be used for such accurate determination. Thus, it is more likely that a parameter will prove that the knowledge included in the prior art is not providing the necessary information for identification. This has the following consequences. If the number of known parameters, e.g., molecular weight, statistical density, or melting point data of a compound[281]is high, the likelihood of novelty is low. If a variety of parameters and structural characteristics of a protein are already known in the prior art, it is not likely that this protein is patentable in terms of novelty at this stage. Even the characterization of the amino acid sequence is not sufficient for compliance with the novelty requirement if the protein is already determined accurately enough so that an unambiguous identification had been possible. Therefore, the description of a patent must not be considered incomplete for the sole reason that specific parameters are not included. The same principle applies with regard to the amino acid sequence. The disclosure of a complete or incomplete amino acid sequence is not a necessary requirement of an unambiguous identification of a protein. [282]

In addition, the level of purification has been an important characteristic of identification in a number of chemical related cases decided by the European Patent Office.[283] In *Interleukin-1/Immunes Corporation,* the opponents alleged that the claimed protein is no more purified than the protein disclosed by the state of the art.[284] The Board acknowledged novelty, however, since there was no evidence that the protein preparation disclosed in the cited documents exhibited features of earlier disclosed inventions, reasoning that it would have been the opponent's burden of proof to provide any corroborating evidence. The proffered unsubstantiated allegations, the Board found, were not based on a comparative analysis and had to be dis-

278 Benkard/Melullis, EPÜ, Art. 54, No. 162-163; Busse/Keukenschrijver, § 3 PateG No. 128.
279 Rauh, Peter A./Jaenichen, Hans-Rainer, Neuheit und erfinderische Tätigkeit bei Erfindungen, deren Gegenstand Protein oder DNA-Sequenzen sind -- Volker Vossius zum 60. Geburtstag, GRUR 1987, 753, 755f.
280 Benkard/Melullis, EPÜ, Art. 54, No. 162-163; Busse/Keukenschrijver, § 3 PateG No. 128.
281 BGH, 3 IIC 226, 235 (1972) – Trioxane.
282 Rauh, Peter A./Jaenichen, Hans-Rainer, Neuheit und erfinderische Tätigkeit bei Erfindungen, deren Gegenstand Protein oder DNA-Sequenzen sind -- Volker Vossius zum 60. Geburtstag, GRUR 1987, 753, 755f.
283 Singer/Stauder, EPC, Vol 1, Art. 54 No. 63.
284 T767/95 Interleukin-1/Immunes Corporation, N. Publ., No. of the Reasons 6.

regarded.[285] In *Vinylester-Crotonsäure/Hoechst,* the Technical Board stated that "a known product does not necessarily acquire novelty merely by virtue of the fact that it is prepared in a purer form", because the prove of novelty "cannot involve properties which are not attributable to the substance parameters of the product itself, i.e. which are not inherent in it.[286] In *Pure terfinadine/Albany* ,[287] the patent applicant attempted to argue that the claimed compound differed from the substances disclosed by the prior art, because it could not be achieved by conventional methods. The Board of Appeals, however, concluded that the applicant did not provide sufficient evidence to support his assertions. In particular, the Board found that the prior art already included small amounts of the substance which were achieved by well-established conventional methods.[288]

If the invention consists of the modification of a known protein, the amended amino acid is considered to satisfy the novelty requirement.[289] The question then arises whether the scope of the patent involving the original protein covers the modified protein. The issue of scope of protection is thoroughly discussed in Part IV of this study.[290] Moreover, the publication of a protein in a protein database is only novelty destroying in the event that the provided information enables a skilled person to isolate such a protein.[291] The same is true for *in silico* screening methods or written formula descriptions.[292]

As reconfirmed by the English House of Lords in *Kirin-Amgen v. TKT*, the new manufacture of a known product is not enough to satisfy the novelty requirement.[293] Here, one of the issues to be resolved was whether the recombinant 'Epo' produced by Amgen was novel or identical to the 'Epo' already part of the state of art, in particular the 'uEpo' which others had purified from urine.[294] Amgen alleged that their recombinant product had a glycosylation pattern differing from the known 'uEpo'. The court, however, denied such assertion, concluding that there was no clear dis-

285 T767/95 Interleukin-1/Immunes Corporation, N. Publ., No. of the Reasons 6-7.
286 T205/83 Vinylester-Crotonsäure Copolymerisate/Hoechst, OJ 1985, 363, 369.
287 T728/98 Pure terfinadine/Albany, OJ 2001, 319. The patent applicant particularly based his arguments on the earlier decision of T990/96 Erythro-compounds/Novartis, OJ 1998, 489.
288 T728/98 Pure terfenandine/ALBANY, OJ 2001, 335; see also Benkard/Melullis, EPÜ, Art. 54, No. 177.
289 T 1208/97 Analogs/AMGEN, N. Publ., No. of the Reasons IX, where the patentee defended novelty based on the argument that the claim feature "has been modified," which"necessarily implied a difference vis-à-vis the natural products."
290 Chapter 4 C IV 1.
291 Benkard/Melullis, EPÜ, Art. 54, No. 164.
292 T1165/06 Il-17 related polypeptide/Schering, N. Publ., No. of the Reasons 21.
293 Kirin-Amgen Inc. and Others v. Hoechst Marion Roussel Limited and Others, [2005] R.P.C. 9; as for the application of this principle in Germany, see Rauh, Peter A./Jaenichen, Hans-Rainer, Neuheit und erfinderische Tätigkeit bei Erfindungen, deren Gegenstand Protein oder DNA-Sequenzen sind -- Volker Vossius zum 60. Geburtstag, GRUR 1987, 753, 756.
294 Kirin-Amgen Inc. and Others v. Hoechst Marion Roussel Limited and Others, [2005] R.P.C. 9, No. 87. The U.S. court decided on this subject in Amgen v. Hoechst Marion Roussel, Inc., 126 F. Supp.2d 69 (D. Mass. 2001), see Welch, Andreas, Der Patentstreit um Erythropoietin, GRURInt. 2003, 579, 593.

tinction between 'uEpo' and the recombinant 'Epo'.[295] Following the approach taken by the EPO that "a new process is not enough to make the product new," the House of Lords concluded that a difference in the method of manufacturing an identical product does not make it novel. Consequently, the House of Lords declared Amgen's claim 26, which defined Epo as the product of recombinant gene expression invalid on the grounds of anticipation.[296]

The decision can be considered a landmark for two reasons. First, it revoked Amgen's claim 26 to recombinant Epo, a product, which had been very successful and powerful on the market for many years. In addition, the House of Lords changed a long existing English practice, which treated a product made by a new process as sufficient to distinguish it from an identical product which was already disclosed in the prior art.[297] Thus, the case demonstrates how national legal principles are given up in favour of standards set forth by the EPO. As stated in the Technical Board decision of *Anspruchskategorien/IFF*, claims to a product defined in terms of a process are only permissible if the product cannot be satisfactorily defined by reference to its composition, structure or other parameter. Otherwise, product-by-process claims are not allowed.[298] Art. 64(2) EPC, however, enables a patentee to rely directly on his process claim to allege infringement of a product made by this process, which is - as concluded by the House of Lords in *Amgen* - "any practical argument for allowing [any other] product-by process claims is removed."[299] Thus, only if Amgen had been capable of proving that their 'Epo' was for the first time produced in a glycols form, the case would have been solved differently. Even though a person skilled in the art would have been able to generally develop a glycols form out of a non-glycols form with the knowledge being included in the state of the art, the glycols form of 'Epo' had not been anticipated. In sum, *Kirin-Amgen v. Hoechst Marion* can be considered an important step towards a harmonization of European patent law.

295 Kirin-Amgen v. Hoechst Marion Roussel, [2005] R.P.C. 9, No. 95.

296 Kirin-Amgen v. Hoechst Marion Roussel, [2005] R.P.C. 9, No. 101.

297 As stated by Lord Hoffman in Kirin-Amgen v. Hoechst Marion Roussel, [2005] R.P.C. 9, No. 88.

298 Anspruchskategorien/IFF, OJ EPO 1984, 309; Benkard/Melullis, EPÜ, Art. 52 No. 119; T 150/82, N. Publ.The House of Lords referred to the European law in Kirin-Amgen v. Hoechst Marion Roussel, [2005] R.P.C. 9, No. 89.

299 Kirin-Amgen v. Hoechst Marion Roussel, [2005] R.P.C. 9, 90; Art. 64(2) EPC states that "[if] the subject-matter of the European patent is a process, the protection conferred by the patent shall extend to the products directly obtained by such process." See also Benkard/Mellulis, EPÜ, Art. 54 No. 174, Benkard/Jestaedt, EPÜ, Art. 64, No. 20.

bb) The principles of second and further medical indications

The development of first and second medical indications for pharmaceuticals by the Enlarged European Board of Appeal of the European Patent office[300] are of major interest for proteomic inventions, since many of these patents may be directed to the treatment of diseases. The following discussion attempts to briefly present the underlying theoretical structure of how novelty is derived from medical indications, keeping in mind the question of whether the principles are transferable to the field of proteomics.[301]

The 2000 EPC revision, put into force on December 13, 2007, led to the amendment of the law related to medical indications.[302] As already mentioned, what used to be the rule under Art. 52 (4) EPC is now added as c) under Art. 53 EPC.[303] Furthermore, the conference established a new version of Art. 54 EPC, including the content of Art. 54 (5) EPC regarding the purpose-related substance protection for the first medical indication in Art. 54 (4). Finally, the provision was extended by a new paragraph (Art. 54(5) EPC), allowing claims for second and further medical indications, and reading as follows:

> "Paragraphs 2 and 3 shall also not exclude the patentability of any substance or composition referred to in paragraph 4 for any specific use in any method referred to in Art. 53(c), provided that such use is not comprised in the state of the art."[304]

Several patents are available for pharmaceuticals under the EPC. Generally, a product patent may be obtained for a substance that provides absolute novelty and matches all further patentability requirements. Absolute novelty requires that the substance be not disclosed in any field of the art. Novelty is established, moreover, if the substance is clearly distinguishable from any known substance by at least a single technical characteristic.[305] In addition, already-known substances are patentable as pharmaceutical means if they were not previously known as agents for treatment or diagnosis. Unlike the U.S., under the EPC, novelty of such a claim, however, cannot be established by method for treatment claims, because Art. 53(c) (former Art. 52(4) EPC) declares methods of treatment and diagnosis practiced on the hu-

300 EBA 1/83, Second medical indication/Bayer, OJ 1985, 60; EBA 5/83, Second medical indication/Eisai, OJ 1985, 64; EBA 6/83, Second medical indication/Pharmuka, OJ 1985, 64; A detailed description is provided by Utermann, Jasper, Der zweckgebundene Verfahrensanspruch für Arzneimittel - Zwei Lösungen für die zweite Indikation, GRUR 1985, 813.

301 As for the scope of protection provided for medical indications, see De Lacroix, Stefan Féaux, Auslegung von Zweckansprüchen in Verfahrenansprüchen - Zweite nichtmedizinische Indikation, GRUR 2003, 282.

302 Nack, Ralph/Phélip, Bruno, Diplomatic Conference fort the Revision of the European Patent Convention. Munich 20 – 29 November 2000, 32 IIC 200 (2001).

303 Chapter 3 A II 1 a) bb).

304 EPO, Special Edition No. 4, OJ 2007, 54; Nack, Ralph/Phélip, Bruno, Diplomatic Conference for the Revision of the European Patent Convention. Munich 20 – 29 November 2000, 32 IIC 200, 204 (2001), Schulte/Moufang, PatG mit EPÜ, §3 Nos. 7-8.

305 Schulte/Moufang, PatG mit EPÜ, § 1, Nos. 250-251.

man or animal body as being excluded from patentability.[306] If previously known substances are useful for methods of treatment and diagnosis, their novelty is rather derived under the principles of first and further medical indications. In this respect, two Enlarged Board of Appeal decisions – still related to the rules valid before the 2000 EPC Revision - must be considered landmarks[307]:

In *Second medical indication/Eisai*[308], the Enlarged Board of Appeals had to decide whether a patent with claims directed to the use of a substance of composition for the treatment of human or animal bodies could be granted. The Board made a distinction between a claim directed to the "use of a substance or composition for the treatment for the human or animal body by therapy" and "a claim directed to the manufacture of substances or compositions for use in any methods for treatment of the human or animal body". The first claim, the Board concluded, does not essentially differ from a claim directed to "a method of treatment of the human or animal body by therapy with the substance or composition" and therefore is clearly in conflict with Art. 52(4) EPC. On the other hand, the latter claim involves without doubt inventions that satisfy the requirement of industrial applicability under Art. 52(1) EPC. The Board emphasized that this is essentially made clear in Art. 52(4) EPC, last sentence, but also can be derived from the definition of "susceptible of industrial application" in Art. 57 EPC, particularly because inventions "can be made or used in any kind of industry, including agriculture". Furthermore, the Board argued with Art. 54(5), according to which the provisions relating to novelty shall not prohibit the patentability of any substance or compositions, comprised in the state of the art, for use in a method referred to in Art. 52(4), provided that its use for any such method is not comprised in the state of the art. Patent protection for such "first medical indication" would be available as a purpose-limited – covering, however, all medical uses, product protection.[309] In a second step, the Board carefully considered the possibility of protecting second and further medical indications by means of a claim directed to the use of a substance or composition for the manufacture of a medicament for a specified (new) therapeutic application.[310] Accepting the practice of the Swiss

306 As for the rational behind former Art. 52(4) EPC that is still applicable to the new Art. 53(c) EPC, see Jaenichen, Hans-Rainer/Mcdonell, Leslie A./Haley, James F., Jr., From Clones to Claims, Cologne, Berlin, Bonn, Munich 2002, 22. The policy behind the exclusion of Art. 52(4) EPC is to ensure that those who carry out surgical, therapeutic, or diagnostic methods as part of the medical treatment of humans or animals should not be hampered by exclusive rights of others; Ricker, Mathias, The exclusion of diagnostic methods from patentability by the EPC: a case for review? 22 Nature Biotechnology 2004, 1167, 1167.

307 As landmark decision of the Technical Board of Appeals of the European Patent office T 385/86, N. Publ., can be considered. Furthermore, the diverging decision T964/99, N. Publ., applies a significantly broader view, Ricker, Mathias, The exclusion of diagnostic methods from patentability by the EPC: a case for review?, Nature Biotechnology, 22 Nature Biotechnology 2004, 1167, 1167.

308 EBA 5/83, Second medical indication/Eisai, OJ 1985, 64.

309 EBA 5/83, Second medical indication/Eisai, OJ 1985, 64, 64-66.

310 EBA 5/83, Second medical indication/Eisai, OJ 1985, 64, 66.

Federal Intellectual Property Office, the Enlarged Board acknowledged patent protection for such claims.

The decision *Second medical indication/Bayer*[311] corresponds to the case law reported above. The Enlarged Board had to decide whether to grant a use patent for a substance of which a therapeutic use had already been included in the prior art. The board rejected the claim directed to the use of a known compound X for the treatment of disease Y, reasoning that such a claim falls under the exclusion from patentability of "methods for treatment of the human or animal body" according to Art. 52(4) EPC. However, it accepted the patent claim directed to the "use of a substance X for the manufacture of a medicament for therapeutic application Y", concluding that novelty of a so-called "Swiss-claim" is determined through the new pharmaceutical use of that known substance.[312] Thus, according to the Enlarged Board, the interpretation of the EPC does not result in general exclusion of second and further medical indications from patentability.

Thus, claims directed to the use of a substance or composition for the design of a new drug with new and inventive therapeutic application are legally accepted. Novelty exists due to the new therapeutic use. The inventive step (Art. 56 EPC) is established if a person skilled in the art was not able to suggest such new therapeutic use.[313] In sum, the following patents are available for medical compositions under the EPC:

- A product patent: Pursuant to 54(1)(2) EPC in combination with Art. 53(c) EPC (former Art. 52 (4) EPC), substances or compositions are patentable, even if they are used in diagnostic methods or methods for treatment, provided that they are new and inventive.[314]

- Purpose-related product patent: The provision that indicates the form of claim permissible for a *first* medical indication is Art. 54 (4) EPC (former Art. 54(5) EPC). Accordingly, in the case of a first medical use, i.e., when the invention results in the finding that a certain substance can be used pharmaceutically, a broad claim to a pharmaceutical composition containing the substance is allowed without restriction to the actual identified medical use (first medical indication).[315]

311 EBA 1/83, Second medical indication/Bayer, OJ 1985, 60.

312 Utermann, Jasper, Der zweckgebundene Verfahrensanspruch für Arzneimittel - Zwei Lösungen für die zweite Indikation, GRUR 1985, 813, 813.

313 In T 0254/93 Ortho Pharmaceutical, N. Publ. (EPA 1997) the invention was rejected on grounds of the inventive step requirement, because it merely suggested that the combined administration of two known substancees causes the avoidance of "skinnatropie".

314 Singer/Stauder, EPC, Vol. 1, Art. 52, Nos. 82-87; see also Schulte/Moufang, PatG mit EPÜ, § 1 Nos. 248, 250-252.

315 Singer/Stauder, EPC – Vol. 1, Art. 54, Nos. 96-99; Schulte/Moufang, PatG mit EPÜ, § 1 Nos. 248, 254, noting that the principle of first medical indications should provide incentives

- Use patent: When a further medical use of a substance already known to be pharmaceutically useful is identified, the EPC allows so-called second medical use claims in the Swiss-type format. These claims relate to the new use of an already known substance (second and further medical indication, incorporated in Art. 54(5) EPC).[316]

4. Nonobviousness and Inventive Step

a) U.S. (Nonobviousness)

According to 35 U.S.C. § 103, a patent claim is rejected "if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains".[317] A patent application fails when, at the time the invention was made, the prior art revealed sufficient information for one skilled in the art to produce the invention with "a reasonable expectation of success."[318]Even though obviousness is treated as a

for potential inventors of pharmaceuticals, whose inventive activity does not depend on whether the pharmaceutically used substance was absolutely new or merely new in the field of medicine.

316 The principle of second and further medical indications determine how a known drug for the treatment of a particular disease can achieve patent protection for the treatment of other diseases, see Singer/Stauder/Spangenberg, EPC – Vol 1, Art. 54 No. 101.

317 For a detailed overview of the requirement of obviousness and applying case law, see Chisum, Donald, Chisum on Patents, Volume 2, Chapter 5, for an introduction, see particularly § 5.01 As for the perspective of the skilled person of art on nonobviousness, see Eisenberg, Rebecca, "Obvious to whom? Evaluating Inventions from the Perspective of PHOSITA", 19 Berkeley Technology L. J. 885 (2004), with regard to the the Historical Development of the nonobviousness requirement, see Duffy, John F., Rethinking the Prospect Theory of Patents" U.Chi.L.Rev. 439 (2004), see also Velander v. Garner, 348 F.3d 1359, 1363 (Fed. Cir. 2003) (The obviousness requirement is based on "(1) the scope and content of the prior art; (2) the level of ordinary skill in the prior art; and (3) the differences between the claimed invention and the prior art.")

318 Medichem, S.A. v. Rolabo, S.L., 437 F.3d 1157, 1165 (Fed. Cir. 2006) (To be sure, "to have a reasonable expectation of success, one must be motivated to do more than merely to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful" (citation omitted).

question of law,[319] the question of whether the claimed subject matter would have been obvious includes factual findings as "relevant secondary considerations".[320]

Relevant secondary considerations are (1) the scope and content of prior art; (2) the level of ordinary skill in the art; (3) the differences between the claimed subject matter and the prior art; and (4) significant, objective evidence of nonobviousness, such as long-felt need in the art, mercantile success, failure of others, copying, and unexpected results.[321] Secondary considerations must be examined whenever they are present and must be given the same weight as to the primary considerations. The initial burden is on the examiner to mount a *prima facie* case of obviousness based on three criteria: 1) the suggestion or motivation in the reference or common general knowledge to modify the reference; 2) the reasonable expectation of success; and 3) the prior art reference suggesting all the claim limitations. Once the examiner establishes a *prima facie* case, the onus shifts to the applicant to demonstrate that the claimed invention is not obvious.[322] The question of obviousness requires the evaluation of the entire prior art. This is in contrast to the novelty factor, where each element is considered separately. Regarding a claim to a DNA or cDNA molecule, the prior art must disclose a teaching of a specific, structurally definable compound that provides the obvious motivation or suggestion to alter the known compound. Accordingly, *prima facie* obviousness exists, if the prior art at least gives a reasonable expectation of success. This includes guidance, which is sufficiently specific to draw

319 Richardson-Vicks Inc. v. Upjohn Co., 122 F.3d 1476, 1479 (Fed. Cir. 1997) (The ultimate conclusion of whether a claimed invention would have been obvious is a question of law reviewed de novo based on underlying findings of fact reviewed for clear error.)

320 Pfizer v. Apotex, 480 F.3d 1348, 1372 (Fed. Cir. 2007), ("Although secondary considerations must be taken into account, they do not necessarily control the obviousness conclusion." (citation omitted)); Eli Lilly and Co. v. Zenith Goldline Pharmaceuticals, Inc., 471 F.3d 1369, 1380 (Fed. Cir. 2006) ("Among other things, Lilly proved extensive secondary considerations to rebut obviousness").

321 Syntex (U.S.A.) LLC v. Apotex, Inc., 407 F.3d 1371, 1378 (Fed. Cir. 2005), (the secondary consideration of commercial success exists largely to provide a means for patentees to show in close cases that subject matter that appears obvious is in law unobvious because a high degree of commercial success permits the inference that others have tried and failed to reach a solution (citation omitted); Graham v. John Deere Company of Kansas City, 383 U.S. 1, 17-18 (U.S. Supreme Court 1966), ("Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented. As indicia of obviousness or nonobviousness, these inquiries may have relevancy."). See also Chisum, Donald, Chisum on Patents, Volume 2, § 5.05[1] (Long-Felt Need - Failure to Others), [2] (Commercial Success), [5](Copying).

322 In re Kumar, 418 F.3d 1361, 1366 (Fed. Cir. 2005) („In patent examination context, the prima facie case is a procedural tool requiring that examiner initially produce evidence sufficient to support a ruling of obviousness, after which burden shifts to applicant to come forward with evidence or argument in rebuttal."); In re Harris, 409 F.3d 1339, 1343 (Fed. Cir. 2005) („When the PTO shows prima facie obviousness, the burden then shifts to the applicant to rebut.") (citation omitted); See also Howlett, Melanie J./Christie, Andrew F., An analysis of the approach of the European, Japanese and United States Patent office to Patenting Partial DNA Sequences (ESTs), 34 IIC 581, 590f (2003).

the attention of someone ordinary skilled in the art to the selection of parameters and choices necessary to obtain the invention, without undue experimentation. Consequently, the prior art that provides the necessary motivation to produce the invention must enable an ordinary skilled person to do so.[323]

Under 35 U.S.C. Section 102(e), a patent is precluded when the "invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant." In *Hazeltine Research, Inc.,* the Supreme Court determined that Section 102(e) is considered a source of prior art under Section 103.[324] Accordingly, the content adequately described in an issued United States patent is fully effective as a reference as of the date when the application for the patent was filed. Thus, *Hazeltine* views material as prior art for the purposes of determining obviousness at the time when the material is not available to the public and is still secret.[325] The decision further developed an earlier established doctrine that "delays of the patent office ought not to cut down the effect of what has been done"[326] The Supreme Court in *Hazeltine* concluded that this rationale extended to the determination of prior art pursuant to § 103 as well as for anticipation.[327] The court explained that the prior applicant has "done what he could to add his disclosure to the prior art."[328] *In re Bartfeld*[329] further made clear that "[t]hough not anticipatory, a reference that would otherwise qualify as prior art under 35 U.S.C. § 102(e) may form the basis of an obviousness rejection under § 103; hence, §102(e)/§ 103 rejections."[330]

Furthermore, two major decisions concerning the obviousness standard are *Hybritech, Inc. v. Monoclonal Antibodies*[331] and *In re O'Farrell*[332]. The first suggested a

323 In re Inland Steel Co., 265 F.3d 1354, 1364 (Fed. Cir. 2001) (the prior art references identify a common problem … and give explicit guidance tying that parameter to the key parameter of another reference).

324 Hazeltine Research, Inc. v. Brenner, 382 U.S. 252 (1965). See also Eli Lilly and Co. v. Aradigm Corp., 376 F.3d 1352, 1367 (Fed. Circ. 2004) (The examiner rejected all of the claims in Lilly's patent application stating that they were anticipated by, under section 102(e), or in the alternative obvious under section 103(a) with respect to a co-pending patent application claiming the same subject matter.)

325 Hazeltine Research, Inc. v. Brenner, 382 U.S. 252, 254. Compare Riverwood International Corp. v. R.A. Jones & Co., 324 F.3d 1346, 1355-56, 66 (Fed. Cir. 2003).

326 As established in Alexander Milburn Co. v. Davis Bournville, 270 U.S. 390 (1926).

327 Hazeltine Research, Inc. v. Brenner, 382 U.S. 252, 256.

328 Hazeltine Research, Inc. v. Brenner, 382 U.S. 252, 256; see also Chisum, Donald, Chisum on Patents, Volume 2, § 5.03[3][b].

329 In re Bartfeld, 925 F.2d 1450 (Fed. Cir. 1991).

330 In re Bartfeld, 925 F.2d 1450, 1451 n.4 (Fed. Cir. 1991), see also Purdue Pharma L.P. v. Boehringer Ingelheim GmbH, 98 F. Supp.2d 362, 392 (S.D. N.Y. 2000), aff'd, 237 f.3d 1359 (Fed. Cir. 2001) (citing Bartfeld; "a terminal disclaimer is incapable of overcoming a rejection on grounds of obviousness pursuant to 35 U.S.C. §§ 102(e) and 103."); Chisum, Donald, Chisum on Patents, Volume 5, § 5.03[3][b].

331 Hybritech, Inc. v. Monoclonal Antibodies, 802 F.2d 1367 (Fed. Cir. 1986), cert. denied, 480 U.S. 947 (1987)

332 In re O'Farrell, 853 F.2d 894 (Fed. Cir. 1988).

milder approach toward the validity of the claims than the latter.[333] In *Hybritech*, a process patent on a "sandwich assay" for detecting the presence of antigenic substances in fluid samples using monoclonal antibodies was challenged.[334] The district court rejected the claim due to obviousness, relying on prior art disclosing methods to prepare monoclonal antibodies and describing similar assays using conventional polyclonal antibodies.[335] The Federal Court reversed the judgment of invalidity, emphasizing that prior art did not disclose more than "invitations to try monoclonal antibodies in immunoassays" that "do not suggest how that end might be accomplished."[336]

In contrast, the Court in *In re O'Farrell* affirmed the rejection of claims due to obviousness.[337] The claimed invention consisted of a method for producing proteins in bacterial host cells. It involved the insertion of the target gene in a plasmid in the DNA of a bacterial protein, followed by transfer of the protein into the bacterial host. In order to produce the gene for the bacterial protein, the host was prepared to "read through" and to express the target gene. In a further step, the expressed gene encoded a protein consisting of the amino acids derived from the genetic information.[338] The USPTO rejected the patent application under 35 U.S.C. § 103, reasoning that the prior art disclosed so much information regarding the claimed method that the latter would have been obvious to a person skilled in art.[339] The inventor argued that the given prior art would not have rendered the claimed method obvious, given the significant unpredictability in this field of molecular biology. He alleged that the standard given was only a standard of "obvious to try", which would not be sufficient for a rejection.[340] The Court of Appeal for the Federal Circuit agreed that "obvious to try" was not the standard being examined under Section 103. Nevertheless, the court stated, the claim at issue should be considered as obvious, since obviousness does not require absolute predictability of success. The existing possibility of unexpected success would not be sufficient to create nonobviousness.[341]

333 Eisenberg, Rebecca, Patenting the Human Genome, 39 Emory Law Journal 1990, 721-745, 731.

334 Hybritech, Inc. v. Monoclonal Antibodies, 802 F.2d 1367, 1368-69.

335 Hybritech, Inc. v. Monoclonal Antibodies, 802 F.2d 1367, 1371.

336 Hybritech, Inc. v. Monoclonal Antibodies, 802 F.2d 1367, 1380. Disagreement recognized by Singh v. Brake, 222 F.3d 1362, 1369 (Fed. Cir. 2000) ("While the witnessing of the laboratory notebooks fell far short of ideal, we do not agree that the belated witnessing undermines all corroborative value that these entries may possess. Under a "rule of reason" analysis, the fact that a notebook entry has not been promptly witnessed does not necessarily disqualify it in serving as corroboration of conception.")

337 In re O'Farrell, 853 F.2d 894.

338 In re O'Farrell, 853 F.2d 894, 895, for a summary, see Eisenberg, Rebecca, Patenting the Human Genome, 39 Emory Law Journal 1990, 721-745, 732.

339 In re O'Farrell, 853 F.2d 894, 901.

340 In re O'Farrell, 853 F.2d 894, 902.

341 In re O'Farrell, 853 F.2d 894, 903-904; Pfizer v. Apotex, 480 F.3d 1348, 1366 (Fed. Cir. 2007) ("Although we recognize some degree of unpredictability of salt formation, the mere possibility that some salts may not form does not demand a conclusion that those that do are necessarily non-obvious." (citation omitted)); Abbott Laboratories v. Andrx Pharmaceuti-

This reasoning was confirmed in *In re Deuel*[342], which involved a patent application referring to DNA and cDNA molecules encoding a protein that stimulates cell division.[343] The Federal Circuit held that the prior art, which included the encoded amino acid and an enabling method for isolating and purifying the DNA, was insufficient to render a claim directed to DNA or cDNA *prima facie* obvious. The court concluded that prior art disclosure of the amino acid sequence of a protein would not automatically make particular DNA molecules encoding the protein obvious because "the redundancy of the genetic code permits one to hypothesize an enormous number of DNA sequences coding for the protein."[344]

The readjustment of the nonobviousness requirement relating to the patenting of DNA process patents is of particular interest for inventions related to the proteomic sector, since it demonstrates how traditional legal standards can be readjusted in order to cope with new technologies such as genomics. Based on the Biotechnological Process Patents Act of 1995, Section 103 was amended, with the result that the *prima facie* obviousness evidence was significantly simplified. The amendment was the final solution of a dilemma that started with the application of principles developed in the field of chemical inventions. In *In re Durden,*[345] a process patent claim concerning a chemical process had been rejected by the USPTO. The patent applicant argued on appeal that while individual process steps were obvious, the use of a novel and nonobvious starting material and the production of a new and nonobvious product implied that the process should be patentable. The Court held that the use of a new starting material and the development of a patented product did not automatically establish the nonobviousness of a process or the grant of a process patent. The Court argued that if every process using a new or novel material was granted a patent, then simple processes such as dissolving or heating would be patentable when using a new compound. This principle however, created a major problem for inventors of a patentable composition of matter who wanted to apply for a biotechnological processes patent making use of the (patented) composition of matter. Inventors of patentable compositions of matter used in a biotechnological process were unable to receive process patents for the use of the patentable composition. This resulted in

cals, Inc., 452 F.3d 1331, 1352 ("The court concluded that they were not so similar as to be interchangeable in the context of polymers like HPMC, correctly rejecting the argument that "obvious to try" can establish obviousness.")

342 In re Deuel, 51 F.3d 1552 (Fed. Cir. 1995).

343 In re Deuel, 51 F.3d 1552, 1554 (Fed. Cir. 1995).

344 In re Deuel, 51 F.3d 1552, 1560. Not followed as dicta in Regents of University of Cal. v. Monsanto Co., 2005 WL 3454107 (N.D.Cal. 2005) ("It is true that one might argue that the cases leave open the question whether disclosure of the complete amino acid sequence of a protein--where specified by unique codons or otherwise described in such a way that knowledge of outside genetic methods could be shown to identify all DNA sequences encoding the protein--can render claims to generic DNA sequences for that protein obvious. Nonetheless, such statements are dictum in both cases, and do not control the decision here."); see also Hoscheid, Dale H./Hemmendinger, Lisa M., Biotechnology and the Federal Circuit, Washington D.C. 2000, 33.

345 In re Durden, 763 F.2d 1406 (Fed. Cir. 1985).

the problem that "unless a patent on the process is obtained (or a patent on the final product), the final product could be prepared overseas and imported back into the U.S. for sale without infringing the patent on the materials used in the process".

For this reason, the U.S. Congress significantly amended Section 103. The revised subsection provides that where a composition of matter meets the novel and nonobvious requirement under main section (103 a), a "biotechnological process" using or resulting in the patentable composition of matter must also be treated as nonobvious if the following five conditions are met.[346]

- The biotechnological process and composition of matter be contained in the same application, separate applications, or separate applications having the same effective filing date;
- both the biotechnological process and composition of matter are owned or subject to an assignment to the same person at the time the process was invented;
- a patent issued on the process also contains the claims to the composition of matter used in or made by the process, or, if the process and composition of matter are in different patents, the patents expire on the same date;
- the biotechnological process falls within the definition set forth in 103(b); and
- a timely election proceeds under the provision of 103(b).[347]

The amendment had a deep impact on the whole field of biotechnological patents. Its effects extend far beyond the process of examination. It establishes absolute protection from the defense in infringement litigation that qualifying biotechnological process claims are construed to be invalid for obviousness.

Another characteristic of the nonobviousness requirement is significant for inventors of protein structures. The application of a strict obviousness standard significantly decreases the risk of permanent and harmful monopoly positions of gene patent holders. Although the USPTO issued several DNA patents based on the general requirements set forth above, it does not imply that the successful identification of a DNA sequence in a gene of interest will remain a nonobvious procedure. Specifically, scientific advances in biotechnology and related fields (such as improved cloning and identification techniques) will likely make future DNA sequences obvious as of the time they are identified. Moreover, advances in protein chemistry have facilitated to an increasing degree the separation, purification, and amino acid sequencing of proteins. Consequently, the cloning and sequencing of genes corresponding to these proteins may become a trivial scientific achievement well established as within the ordinary skill of biotechnological researchers. Claims to newly purified chemicals have often been challenged in the past as obvious relative to naturally existing

346 USPTO Notice, Guidance on Treatment of Product and Process Claims in Light of In re Ochiai, In re Brwouwer and 35 U.S.C. § 103(b), available at http://www.uspto.gov/go/og/con/files/cons104.htm, last checked on January 21, 2008.

347 USPTO Notice, Guidance on Treatment of Product and Process Claims in Light of In re Ochiai, In re Brwouwer and 35 U.S.C. § 103(b), available at http://www.uspto.gov/go/og/con/files/cons104.htm, last checked on January 21, 2008.

impure products. In response, courts upheld the validity of those claims, concluding that nonobviousness was established by the fact that the inventor had shown the difficulty and unpredictability of synthesizing the desired gene. It is, however, likely that patent examiners in the near future will reject any claims to the protein-encoding DNA sequence, provided sufficient information is available regarding the protein corresponding to the gene to enable its synthesis in pure form.[348]

In *Teleflex v. KSR*[349]*,* Teleflex sued KSR arguing that one of KSR's products infringed Teleflex's patent involving an adjustable vehicle control pedal connected to an electronic throttle control. KSR assessed that the connection of the two elements was obvious, and the claim was therefore invalid. The district court ruled in favor of KSR, but the Court of Appeals for the Federal Circuit reversed the judgment.[350]

The Supreme Court reversed the Federal Circuit holding, stating that claim 4 of the patent was obvious under the threshold of 35 U.S.C. §103. The Court found that in "rejecting the District Court's rulings, the Court of Appeals analyzed the issue in a narrow, rigid manner inconsistent with §103 and our precedents," referring to the Federal Circuit's application of a "teaching, suggestion, or motivation" (TSM) test, under which "a patent claim is only proved obvious if the prior art, the problem's nature, or the knowledge of a person having ordinary skill in the art reveals some motivation or suggestion to combine the prior art teachings."[351]

The Supreme Court made clear that "[a] person of ordinary skill is also a person of ordinary creativity, not an automaton."[352] The judge acknowledged that his definition of a person having ordinary skill in the art does not necessarily conflict with other Federal Circuit cases that described a skilled person as having "common sense" and whose incentive was based on "implicitly in the prior art."[353] The judge emphasized that his opinion had the purpose of correcting the "errors of law made by the Court of Appeals in this case" and does not necessarily overturn all other Federal Circuit rulings.[354]

348 Eisenberg, Rebecca, Patenting the Human Genome, 39 Emory Law Journal 1990, 721-745, 730-731.
349 Teleflex, Inc. v. KSR International, 127 S. Ct. 1727 (Fed. Cir. 2007).
350 Teleflex, Inc. v. KSR International, 127 S. Ct. 1727, 1727.
351 Teleflex, Inc. v. KSR International, 127 S. Ct. 1727, 1729.
352 Teleflex, Inc. v. KSR International, 127 S. Ct. 1727, 1742.
353 Teleflex, Inc. v. KSR International, 127 S. Ct. 1727, 1743.
354 Teleflex, Inc. v. KSR International, 127 S. Ct. 1727, 1743.

With regard to a general standard of obviousness, the Court ruled:

> "One of the ways in which a patent's subject matter can be proved obvious is by noting that there existed at the time of invention a known problem for which there was an obvious solution encompassed by the patent's claims."[355]

When the requirements for obviousness were applied to the question at issue, however the Court stated:

> "ordinary skill, facing the wide range of needs created by developments in the field of endeavor, would have seen a benefit to upgrading [the technology disclosed by the prior art] with a sensor.[356] "

Hence, the court defined the recognition of a benefit as the crucial factor for any obviousness evaluation. This is, however, a different approach than asking whether someone had been motivated to make a chance, a threshold applied in earlier decisions.

The decision started an intense debate over the impact on the TSM test and the earlier used "obvious to try" standard. This was particularly because, even though the Supreme Court did not reject the TSM test in general, it had referred to it with some critical language. More specifically, the judge found that obviousness

> "must not be confined within a test or formulation too constrained to serve its purpose."[357]

Generally, *KSR* ruled against the approach restricting the use of a "common sense", denying "rigid preventatives rules that deny factfinders recourse to common sense".[358]

The judge, however, made clear that the TSM test remains applicable to the question of obviousness, emphazising, however, that the manner in which the test is to be applied is newly instrued."[359]

In *Leapfrog Enterprises, Inc. v. Fisher-Price, Inc.*, (Fed. Cir. May 9, 2007), the Federal Circuit interpreted the *KSR* case, holding the patent under review was invalid for being obvious.[360] Accordingly, even though *Teflex* did not suddenly make all inventions obvious, *Leapfrog* shows that the *Teflex* approach is the now applied standard for defining obviousness.

b) Europe (Inventive Step)

Pursuant to Art. 56 EPC, an invention shall be considered as involving an inventive step if, having regard to the state of the art, it is not obvious to a person skilled in the

355 Teleflex, Inc. v. KSR International, 127 S. Ct. 1727, 1742.
356 Teleflex, Inc. v. KSR International, 127 S. Ct. 1727, 1744.
357 Teleflex, Inc. v. KSR International, 127 S. Ct. 1727, 1746.
358 Teleflex, Inc. v. KSR International, 127 S. Ct. 1727, 1742-1743.
359 Teleflex, Inc. v. KSR International, 127 S. Ct. 1727, 1741.
360 Leapfrog Enterprises, Inc. v. Fisher-Price, Inc., 485 F.3d. 1157 (Fed. Cir. 2007).

art. In this respect, the prior art is considered as a whole, i.e., the teachings of separate prior art documents are combined together.[361]

Several tests are used to determine inventive activity, such as the problem-solution approach[362] and the "could/would" test[363]. Indications for inventive activity include commercial success, surmounting of difficulties, disbelief and scepticism of experts, satisfaction of long existing needs and the finding of new and unexpected results.[364] The relevant moment for determination is the filing/priority date and no *ex post facto* judgement is allowed.[365]

The finding of unexpected results often occurs in the field of chemicals or pharmaceuticals, where surprising effects or characteristics of substances are the outcome of experimentation.[366] Such surprising characteristics can include, for example, reduced side effects, improved resorption and stability of the new protein. Even if the isolation as such is not inventive, the surprising effect is sufficient to establish inventiveness.[367]

In the field of chemical inventions, *Triazole/Agrevo*[368] can be considered a major decision, in which the problem-solution-approach of the EPO was defended and approved against the appellant's allegation that Art. 56 EPC did not expressly require that the subject matter of a patent application had to solve a technical problem. The Board of Appeals defined the "problem-solution-approach" as a "generally accepted legal principle" and held that the technical effect of the claimed invention is inherently connected to the determination of inventive step. The Board stated that what the skilled person would have done depends on the technical result they set out to achieve rather than "idle curiosity". Lacking the solution to a technical problem, an

361 Benkard/Jestaedt, EPÜ, Art. 56, No. 1. This differs from the examination of novelty, where it is not permissible to combine separate prior art documents together, see Chapter 3 A II 3 b); T 153/85, OJ 1988, 1 "Alternative Claims".

362 The test asks whether a person skilled in the art not only theoretically "could" have prepared the claimed compounds, but whether he "would" have done so in view of the state of the art; Szabo, George S. A , The Problem and Solution Approach in the European Patent Office, 26 IIC 457 (1995).

363 T 513/90, Geschäumte Körper/Japan Styrene, OJ 1994, 154, 160f.; T 455/91 Expression in Yeast/Genentech, OJ 1995, 684, 730f; Guidelines for Examination in the EPO, Part C-IV, 9.10.2.

364 Kraßer, Rudolf, Patentrecht: ein Lehr- und Handbuch zum deutschen Patent- und Gebrauchsmusterrecht, europäischen und internationalen Patentrecht, 5. Aufl., München 2004, 325-332.

365 The desisive question is whether the person skilled in the art had been able to carry out the invention on the priority date without any inventive activity, see Busse/Keukenschrijver, PatG, § 4, No. 24.

366 Busse/Keukenschrijver, PatG, § 4, No. 16, emphasize that an element is interpreted as a very strong sign for inventive activity.

367 T 181/82 Spiroverbindungen/Ciba-Geigy, OJ 1984, 401, 409; T 57/84 Tolylfluanid/Bayer, OJ 1987, 53; T 939/92; OJ 1996, 309, 317. The fact that a chemical substance's property was distinct from other chemical substances had been surprising for a person skilled in the art may be sufficient to establish inventive activity, see Busse/Keukenschrijver, PatG, § 4, 89.

368 T 939/92, Triazone/Agrevo, OJ 1996, 309, 317.

invention would probably not involve any inventive step. The case dealt with claims for chemical compounds. The Board held that an arbitrary selection of chemical compounds that were structurally similar to the closest prior art could not involve any inventive step. For the assessment of the inventive step, the examiner must study the claim, the closest prior art, and the difference in terms of features of the claim and the closest prior art. Then the examiner must determine whether the conclusion of all of the closest prior art documents would prompt the skilled person, faced with the technical problem, to adapt the closest prior art to arrive at something within the terms of the claim. The inventive step criteria must be examined in relation to all aspects of the claimed invention, including the underlying problem, the insight upon which the solution relies, the means constituting the solution, and the effect or results obtained. The ruling clearly describes the method of the "problem-solution-approach", describing the three main stages: e.g., determining the "closest prior art"; establishing the "objective technical problem" to be solved; and considering whether or not the claimed invention, starting from the closest prior art and the objective technical problem, would have been obvious to the skilled person.[369]

With regard to the recombinant production of proteins, *Human beta-interferon/BIOGEN*[370] is an example of how the requirement of inventive step is analyzed. The Board of Appeal rejected a claim to a recombinant produced polypeptide displaying the immunological or biological activity of human beta-interferon (β-IFN) for lack of an inventive step. The examiners concluded that the construction of the β-IFN expression vector *per se* does not require more than routine effort from the average skilled person. A skilled person could have reasonably expected the beta-IFN cDNA to be expressed in the recombinant host as an active protein. Thus, the known properties of the human β-IFN contained a clear and obvious suggestion as to how to produce it.[371]

In *Milk production/MONSANTO*[372], the EPO adopted the U.S. standards of analyzing the obviousness requirement that had been established in *In re O'Farrell*. As in *In re O'Farrell*, the appellant alleged that a standard of "obvious to try" would not be sufficient for a rejection. The court followed the U.S. patent law by stating that obviousness does not require absolute predictability of success. The court clarified that the need of experimentally confirming a reasonably expected result does not render an invention unobvious, determining that, in the case at issue, an average skilled person was provided "with a clear hint from the prior art pointing him in the direction of the claimed method."[373]

In sum, the European inventive step requirement is very similar to the U.S. law on obviousness: a patent claim lacks inventive activity if every element of the claim is included or suggested by the state of the art. The state of the art as such must pro-

369 T 939/92, Triazone/Agrevo, OJ 1996, 2.4 – 2. 7.
370 T 207/94 Human beta-interferon/BIOGEN, N. Publ.
371 T 207/94 Human beta-interferon/BIOGEN, N. Publ., No. of the Reasons, 22-44.
372 T 249/88, Milk production/MONSANTO, N. Publ.
373 T 249/88, Milk production/MONSANTO, N. Publ., No. of the Reasons, 8.

vide the motivation to combine several references to meet the claims. In the U.S., the decision of *In re Deuel*, however, made clear that prior art does not render a claim obvious, if the skilled person is permitted "to hypothesize an enormous number" of possibilities to carry out the invention.[374]

5. Written description/patent description and sufficient disclosure

Compared to other patentability requirements, the need to provide a written description fulfilling certain minimum standards (in the case of the U.S.) and to suffciently disclose the invention (in the case of Europe) has long been considered an issue of a somewhat lower importance. This has changed in recent years, not least as a consequence of the increasing complexity of explaining and demonstrating the nature and scope of biotechnological patents.

a). U.S.

In particular in the U.S., a controversial debate about whether and in what form patent law princples imply a "seperate" written description requirement has emerged. A review of this debate offers important lessons, not only for inventors of proteomic structures. Before going through the arguments that have dominated the discussion, the following section will first outline the basic statutory background, focusing on cases with a biotechnological subject matter.

aa) Basic statuatory background

Pursuant to Section 35 U.S.C. § 112(1), a patent application shall

> "contain a written description of the invention, and of the manner and process of making and using it in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention."

The provision can be seen as containing four individual requirements, usually denominated as: (1) written description, (2) enablement, (3) best mode and (4) definiteness[375]. However, as discussed in detail below, the Federal Circuit has not decisively clarified whether the written description requirement must be considered separately from enablement and best mode.

374 In re Deuel, 51 F.3d 1552, 1560. See Chapter 3 A II 4 a).

375 See Guidelines for Examination of Patent Applications under the 35 U.S.C. § 112, 1, "Written description" Requirement, 66 Fed. Reg. 1099, 1014 (Jan. 5, 2001) [hereinafter Written Description Guidelines].

The requirement of enablement demands that the applicant's specification provides sufficient disclosure about the invention. Generally, the specification must provide enough instruction so that a person skilled in the art would not have to exercise any "undue experimentation"[376] to make and use the full scope of the claimed invention.

In re Wands set forth the details of enabling.[377] In this decision, a patent application, referring to the disclosure of immunoassay methods for detecting the hepatitis B virus using high-affinity immunoglobulins, was rejected. The court stated that the application did not enable one to make and use the claimed invention. On appeal to the CAFC, the patentee argued that the application in fact was enabling because a DNA encoding the high-affinity immunoglobulin had been deposited with the American Type Culture Collection (ATCC) and was accessible to the public. Consequently, a person skilled in the art would not have had to perform undue experimentation to make the antibodies necessary for the claimed invention. The CAFC agreed that the patent application was complying with the enablement factor. In the decision, the court stressed the factors that should be considered when determining whether undue experimentation would be required to practice a claimed invention. The so-called *Wands factors* include:

- The quantity of experimentation necessary to practice the claimed invention;
- the amount of direction or guidance presented in the specification;
- the presence or absence of working examples in the specification;
- the nature of the invention;
- the state of the prior art
- the relative skill of those of ordinary skill in the art
- the predictability or unpredictability of the art; and
- the breadth of the claims.[378]

Amgen, Inc. v. Chugai Pharm. Co. shows how the Federal Circuit applies the patent jurisprudence relating to chemical compounds to biotechnology, and provides a framework for the treatment of enablement in cases involving nucleic acid sequences.[379] Amgen was the owner of a patent to a purified and isolated DNA sequence encoding the human erythropoietin ('Epo') gene. The district court invalidated a claim covering a "potentially enormous" number of 'Epo' analogs for lack

376 In re Wands, 858 F.2d 731, 731 (Fed. Cir. 1988). See also Kunin, Stephen G/ Nagumo, Mark/ Stanton, Brinaet al., Reach-through claims in the age of biotechnology, 51 American University Law Review April 2002, 609-638, 630.

377 In re Wands, 858 F.2d 731 (Fed. Cir. 1988).

378 In re Wands, 858 F.2d 731, 731.

379 Amgen, Inc. v. Chugai Pharm. Co., 927 F.2d 1200, 1206, 1212. (Fed. Cir. 1996) ("A gene is a chemical compound, albeit a complex one, and it is well established in our law that conception of a chemical compound requires that the inventor be able to define it so as to distinguish it from other materials, and to describe how to obtain it.")

of enablement.[380] The Federal Circuit confirmed that the claims were not enabled, but instead based its conclusion on the lack of enablement of the underlying DNA sequences. The court explained:

> "It is not necessary that a patent applicant test all the embodiements of this invention; what is necessary is that he provides a disclosure sufficient to enable one skilled in the art to carry out the invention commensurate with the scope of the claims. For DNA sequences, that meant disclosing how to make and use enough sequences to justify grant of the claims sought. Amgen had not done that here."[381]

In *In re Fisher*,[382] the Federal Circuit confirmed the rejection of enablement, "because the claimed ESTs were not disclosed as having a specific and substantial utility."[383] According to the court "it is well established that the enablement requirement of § 112 incorporates the utility requirement of § 101."[384]

In *Falko-Gunter Falkner v. Inglis*,[385] the patent application claimed a novel type of vaccine production applicable to various types of "vector viruses", such as adenoviruses, herpesviruses, poxviruses and retroviruses. In vaccinations using vector viruses, immunity against the target virus is achieved by exposing the immune system to harmless fragments of the target virus. To prevent infections through the viral vector itself, genes that cause a vector's harmful effects have to be inactivated, traditionally by deleting an *inessential* gene from the respective genome. By devising a method in the course of which an *essential* gene is inactivated, the inventors claimed to have discovered a substantially safer way of vaccine production. Moreover, the new method offered a solution to a fundamental problem of vaccine production. By growing vaccines in cells that were complementarily modified to produce the absent essential viral gene product "on behalf of" the vector virus, the difficulty of growing an inhibited or "attenuated" version of a virus was effectively circumvented.

While being applicable to the various viruses mentioned above, the patented invention dealt specifically with vaccines in which the vector virus is a *poxvirus*.[386] The specification, however, provided a detailed example of an embodiment that comprised herpes virus, not poxvirus, including identity of deleted essential se-

380 Amgen, Inc. v. Chugai Pharm. Co., 927 F.2d 1200, 1204.
381 Amgen, Inc. v. Chugai Pharm. Co., 927 F.2d 1200, 1212.
382 In re Fisher, 421 F.3d 1365 (Fed. Cir. 2005). For a summary of the factual background and the court's ruling regarding the utility requirement, see Chapter 3 A II 2a.
383 In re Fisher, 421 F.3d 1365, 1378.
384 In re Fisher, 421 F.3d 1365, 1378, (citations omitted); see also In re Kirk, 376 F.2d, 936, 942 (C.C.P.A. 1967) ("Necessarily, compliance with § 112 requires a description of how to use presently useful inventions, otherwise an applicant would anomalously be required to teach how to use a useless invention."); In re Brana, 51 F.3d 1560, 1564 (Fed. Cir. 1995) ("Obviously, if a claimed invention does not have utility, the specification cannot enable one to use it.").
385 Falko-Gunter Falkner v. Inglis, 448 F.3d 1357 (Fed. Cir. 2006).
386 Falko-Gunter Falkner v. Inglis, 448 F.3d 1357, 1360.

quences therein. The Federal Circuit nevertheless concluded that the patent was adequately enabled, and explained:

> "[T]here is extensive disclosure of the selection of an essential gene, its deletion or inactivation and the production of a mutated virus with said deleted or inactivated gene, albeit for herpesvirus." Moreover, because the differences between the herpesviruses and poxviruses were well known, this would have aided the person of ordinary skill in the art in her application of the lessons of the herpesvirus example in the construction of poxvirus vaccines. … the mere fact that the experimentation may have been difficult and time consuming does not mandate a conclusion that such experimentation would have been considered to be 'undue' in this art. Indeed, great expenditures of time and effort were ordinary in the field of vaccine preparation."[387]

The court declared that a skilled person was clearly considered to be able "to identify the 'essential' poxvirus genes [by] relying on publications in professional journals that had disclosed the DNA sequence of the poxvirus genome along with the locations of the 'essential regions,'… since a patent need not teach, and preferably omits, what is well known in the art."[388]

bb) Deposit requirements

In order to overcome the difficulty of providing a detailed written description sufficient to permit the production of complex living organisms, the courts accepted as a substitute the deposit of living material with a public depository. Public access to the deposited material was determined to be sufficient to satisfy Section 112, first paragraph.[389] This solution was established in *In re Argoudelis*.[390] The United States Court of Customs and Patent Appeals (CCPA) assumed that "there can be no description in words alone of how to obtain the microorganism from nature".

A deposit was sufficient to satisfy the enablement requirement of Section 112, first paragraph, if (1) a public depository was used, (2) the deposit was made prior to the filing date of the application, (3) the depository and accession number were referenced in the application as filed, (4) the depository was under a contractual obligation to maintain the deposited culture in the permanent collection, (5) the depository was under obligation to supply samples to persons having access to the pending application, (6) the deposited organism would be made available to the public without restriction on the issue date of the patent, and (7) the cultures were not expected to undergo any physical changes rendering them unusable.[391]

387 Falko-Gunter Falkner v. Inglis, 448 F.3d 1357, 1365.
388 Falko-Gunter Falkner v. Inglis, 448 F.3d 1357, 1365, citing Spectra-Physics, Inc. v. Coherent, Inc., 827 F.2d 1524, 1534 (Fed. Cir. 1987).
389 Monsanto Co. v. Scruggs, 459 F.3d 1328, 1337 (Fed. Cir. 2006) (The written description requirement was satisfied because the '605 patent incorporates by reference deposits with the American Type Culture Center, which are publicly available.)
390 In re Argoudelis, 434 F.2d 1390 (C.C.P.A. 1970).
391 In re Argoudelis, 434 F.2d 1390, 1394.

In *Feldman v. Aunstrup*[392], the court stated that the requirements established in *Argoudelis* were not mandatory. More specifically, a deposit in private foreign entities was deemed sufficient under Section 112. The essential criteria, the court reasoned, were that the culture was permanently available, and that access was assured. In I*n re Lundak*, the court concluded that even the "deposit" of a microorganism in the inventor's private laboratory may meet the standard of Section 112 at the time of filing, and that public depository is sufficient if it is made at any time prior to the issuance of the patent.[393] The court further held that neither the postfiling depository nor the addition of the accession number to the pending application enlarges the disclosure of the specification by the addition of new matter.[394]

cc) The debate on a separate written description requirement

i. Background to the debate

Soon after broad biotechnological claims had become standard practice, concerns were raised about their medium- and long-term effects on product innovation.[395] In the ensuing debate about how to prevent overly broad claims, proposals ranged from legislative changes to a stricter approach to patent specification requirements.[396] With respect to the latter, a number of landmark decisions of the Federal Circuit Court further attracted substantial interest. A majority of Federal Circuit judges interpreted Section 112, first paragraph of the U.S. Patent Act as imposing a "separate written description requirement". More specifically, "written description" was seen as a requirement distinct from "enablement", a view that has inspired an intense dispute over the appropriateness of alternative patent drafting strategies and the legal certainty that can be reasonably expected when possessing a patent. Due to its wide-ranging implications and its importance for the debates on the appropriate scope of protection, it is essential to review the court's decision extensively.[397]

In several cases, the majority of judges concluded that a patent serves not only to disclose to the public how to 'make and use' an invention, but also to indicate whether the inventor actually "possessed the invention" at the time the application was filed. Accordingly, an analysis pursuant to Section 112 would ask for two sepa-

392 Feldman v. Aunstrup, 517 F.2d 1351, 1352 (C.C.P.A. 1975).
393 In re Lundak, 773 F.2d 1216, 1222 (Fed. Cir. 1985).
394 In re Lundak, 773 F.2d 1216, 1223.
395 See, for example, Schiermeier, Quirin, German agencies sound alarm on risks of broad gene patents, Nature 406, 2000, 111.
396 Barton, John H., United States Law of Genomic and Post-Genomic Patens, 33 IIC 779, 782 (2002), noting that after the Ely Lilly decision it is unlikely that a gene can be patented without identification of its sequence.
397 Mull, William C., Using the Written Description Requirement to Limit Broad Patent Scope, Allow Competition, and Encourage Innovation in Biotechnology, 14 Health Matrix: Journal of Law-Medicine 2004, 393, 393ff.

rate and independent requirements. First, the applicant must describe the invention so that a person skilled in the art can recognize the claim as what has actually been invented (i.e., actually or constructively "possessed"). Second, the description has to be drafted in a way that enables the public to make and use the full scope of the invention."[398]

A minority of Federal Circuit Judges, headed by Judge Rader, strongly opposed the majority view, rejecting the appropriateness and legal consistency of a "separate written description requirement". Without regard to enablement, the content of the written description and its adequacy to support the claims should only be considered in cases related to priority, but not in the context of patentability. In the view of the minority, such a reading would be consistent with earlier rulings by the Federal Circuit, which only examined enablement and best mode under §112.[399] It would also be sufficient to accommodate Section 132, which prohibits the addition or amendment of claims subsequent to the effective filing date that would add new matter to the application.[400]

398 Amgen Inc. v. Transkaryotic Therapies, Inc., 314 F.3d 1313, 1330 (Fed. Cir. 2003). In Regents the University of California v. Eli Lilly & Co., 119 F.3d 1559 at 1566 (Fed. Cir. 1997), the Federal Circuit clearly determined that the § 112 analysis "requires a precise definition, such as by structure, formula, chemical name, or physical properties, not a mere wish or plan for obtaining the claimed … invention." In Amgen, 314 F.3d at 1332 (Fed. Cir. 2003), the threshold was narrowed down by the Federal Circuit's statement that "Eli Lilly did not hold that all functional descriptions of genetic material necessarily fail as a matter of law to meet the written description requirement, rather, the requirement may be satisfied if the knowledge of the art of the disclosed function is sufficiently correlated to a particular, known structure." Capon v. Eshhar, 418 F.3d 1349, 1360 (Federal Circuit 2005) weakened the Eli Lily doctrine much further with the statement that "[t]he predictability or unpredictability of the science is relevant to deciding how much experimental support is required to adequately describe the scope of an invention." Capon, however, fails to establish clear rules of how broad a patent specification must be drafted. Even though it states that prior art must be taken into account, more detailed information of how far this prior art consideration must be made, is missing.

399 In re Gay, 50 C.C.P.A. 725, 309 F.2d 769, 772 (C.C.P.A. 1962). Originally, courts considered claims part of the disclosure, which is why they could not lack adequate description, see In re Smith, 481 F.2d 910, 914 (C.C.P.A. 1973) ("Where the claim is an original claim, the underlying concept of insuring disclosure as of the filing date is satisfied, and the description requirement has likewise been held to be satisfied.")

400 In Enzo Biochem., Inc. v. Gen-Probe International, 323 F.3d 956 at 977 Judge Rader starts his analysis with a detailed review of the origin and history of the written description requirement ("[E]very patent system must have some provisions to prevent applicants from using the amendment process to update their disclosure (claims or specification) during their pendency before the patent office). In contrast, the judge refuses to analyse the written description in cases in which priority is not in question, Id. at 979 ("[W]ritten description does not examine the specification for 'literal support' of the claim language unless priority is in question."). Chiron v. Genentech, 963 F.3d 1247 at 1255 (Fed. Cir. 2004) also exemplifies how the written description requirement is examined in the context of priority. ("[T]he written description requirement prevents applicants from using the amendment process to update their disclosures.").

The implications of these alternative solutions are wide-ranging. In particular, a 'separate written description requirement' forces applicants to provide a much more detailed delineation of the nature, scope, and application of claims.[401] Moreover, it is likely that certain subject matter cannot be patented until a later stage of understanding of the invention and its potential embodiments. Similar to the utility requirement, an additional written description requirement may thus force inventors to delay the filing of a claim, while at the same time limiting the broadness of a claim. This is particularly relevant for biotechnological inventions, as many generic inventions may be enabled without a clear understanding of what the claim actually applies to.

ii. Development of a 'separate written description' doctrine

In *Regents of the University of California v. Eli Lilly & Co*[402], the Federal Circuit held cDNA encoding rat insulin to be an insufficient written description to support claims to cDNAs encoding vertebrate, mammalian, or human insulin, even though the application included a method to isolate those cDNAs. The court clarified that "describing a method or preparing a cDNA or even describing the protein that the cDNA encodes does not necessarily describe the cDNA itself."[403] A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, whose features constitute a substantial portion of the genus.[404] Thus, the court concluded, the § 112 analysis "requires a precise definition, such as by structure, formula, chemical name, or physical properties, not a mere wish or plan for obtaining the claimed chemical invention", but "none of those descriptions appeared in that patent."[405]

The reasoning of *Ely Lilly* was adapted in further cases. In *Carnegie Mellon v. Hoffman-La Roche*[406], a district court held that claims referring to plasmids for the controlled expression of DNA polymerase I derived from any bacterial source were invalid because the specification only described DNA polymerase I from E.coli. The court argued that the *Lilly* decision was applicable, stating that "there is nothing in the *Eli Lilly* decision to suggest that the Federal Circuit's observations about the na-

401 Under Section 112, the applicant is required to disclose what he "regards as the invention." Thus, although the disclosure may be used to help interpret the claims, the disclosure may evidence a variance from the nature of the invention that the applicant actually believed was invented (and thus was possessed at the time of filing). Although inquiry may still be made into such differences between claim meaning and the invention during prosecution, they are no longer able to be raised in litigation to challenge the validity of the claims. See Solomon v. Kimberley Clark Corp., 216 F.3d 1372, 1377 (Federal Circuit 2000).

402 Regents of the University of California v. Eli Lilly & Co., 119 F. 3d 1559 (Fed. Cir. 1997).

403 Regents of the University of California v. Eli Lilly & Co., 119 F. 3d 1559, 1567.

404 Regents of the University of California v. Eli Lilly & Co., 119 F3d. 1559, 1569.

405 Regents of the University of California v. Eli Lilly & Co, 119 F.3d 1559, 1566.

406 Carnegie Mellon v. Hoffman-La Roche, Inc.; 148 F. Supp. 2d 1004 (N.D. Cal. 2001).

ture of DNA was applicable only to novel DNA and not to any DNA sequence. A similar finding is established in *Bristol-Myers Squibb v. Rhone-Poulenc er.*[407]Here, the district court held that a generic claim must be rejected because the patentee failed to provide a copy of a scientific article by the inventors indicating that they themselves did not believe the invention could be practiced as broadly as claimed. Therefore, inventors should warrant that the extent of the claims is commensurate with the underlying science.

Enzo Biochem v. Gen-Probe[408] is another landmark decision in which the strict written description requirement was confirmed. In the case, the CAFC considered a patent directed to three nucleic acid probes that hybridize preferentially with the DNA of the bacterium causing gonorrhea. The broader claims of the patent recited the probes as binding preferentially to the gonorrhea organism rather than a closely related one. The court argued that because the patentee had described the probes only in terms of sequence function (preferential hybridization), the written description for the claimed invention was inadequate as a matter of law. The court considered that although a "description of the ability of the claimed probe to bind to N. gonorrhoeae may describe that probe's function, it does not describe the probe itself. We reject *Enzo's* characterization of the hybridization as a distinctive 'chemical property' of the claimed sequence." Therefore, it is inadequate to describe genetic material by what it does, such as hybridizing with N. gonorrhoeae, notwithstanding the labeling of the described property as "chemical" or "functional".

In *University of Rochester v. Searle et al.*,[409] the patentee claimed a method for selectively inhibiting the activity of a particular protein by "administering a nonsteroidal compound that selectively inhibits activity of that protein in a human in need of such treatment". The University of Rochester sought to enforce its patent relating to the "new generation" of pain relievers, which act selectively through the

407 Bristol-Myers Squibb v. Rhone-Poulenc Rorer, 2001 WL 1512597.

408 Enzo Biochem v. Gen-Probe, 323 F.3d 956 (Fed. Cir. 2002). The Federal Court ruled on the issue in a number of further decisions. For the direct history of the case, see Enzo Biochem, Inc. v. Gen-Probe Inc., 285 F.3d 1013, 62 (Fed. Cir. 2002). Opinion Vacated on Rehearing by Enzo Biochem, Inc. v. Gen-Probe Inc., 323 F.3d 956 (Fed. Cir. 2002). For Additional Opinion, see Enzo Biochem, Inc. v. Gen-Probe, Inc., 2002 WL 32063710, 63 U.S.P.Q.2d 1618 (Fed. Cir. 2002) AND Appeal After Remand Enzo Biochem, Inc. v. Gen-Probe Inc., 414 F.3d 1376 (Fed. Cir. 2005). Order Recalled and Vacated by Enzo Biochem, Inc. v. Gen-Probe Inc., 143 Fed. Appx. 350 (Fed. Cir. 2005) (Not selected for publication in the Federal Reporter).

409 University Of Rochester v. G.D. Searle & Co., Inc., 358 F.3d 916 (Fed.Cir. 2004). The Federal Circuit decided on the issue in a number of further decisions, see University of Rochester v. G.D. Searle & Co., Inc., 249 F.Supp.2d 216 (W.D.N.Y. 2003). Decision Affirmed by University Of Rochester v. G.D. Searle & Co., Inc., 358 F.3d 916 (Fed. Cir. 2004). Rehearing and Rehearing en banc denied by University of Rochester v. G.D. Searle & Co., Inc., 375 F.3d 1303 (Fed. Cir. 2004) AND Certiorari denied by University of Rochester v. G.D. Searle & Co., Inc., 543 U.S. 1015 (2004).

409 Warburg, Richard J./Wellman, Arthur/Buck, Todd/Ligler Schoenhard, Amy E., Patentability and Maximum Protection of Intellectual Property in Proteomics and Genomics, 22 Biotechnology Law Report 2003, 264, 269.

inhibition of COX-2. By doing so, these pain relievers achieve the desired effect (inhibition of pain) while avoiding some of the undesirable side effects (particularly stomach irritation) invoked by earlier pain relievers which inhibit both COX-2 and COX-1. The patent disclosed and claimed methods for screening compounds to identify those that selectively inhibited the COX-2 gene product while having minimal effect on COX-1 activity, and the specification identified a single compound (NS-398) which is a specific inhibitor of COX-2 activity.[410]

The district court found the claims to be invalid for lack of an adequate written description, concluding that the patent did not disclose a specific compound, and provided no guidance on how to make or obtain any compound that fell within the scope of the patent's claim." [411] On appeal, the University contested the district court's ruling that a claim drawn to a method of obtaining a biological effect in a human by administering a compound cannot, as a matter of law, satisfy the written description requirement without disclosing the identity of any such compound.[412] The Federal Circuit rejected this argument, stating that an adequate written description requirement would "describe the claimed invention so that one skilled in the art can recognize what is claimed."[413] Generalized language may be inadequate if it does not convey the detailed identity of an invention. The court explained that "[r]egardless whether a compound is claimed *per se* or a method is claimed that entails the use of the compound, the inventor cannot lay claim to that subject matter unless he can provide a description of the compound sufficient to distinguish infringing compounds from non-infringing compounds, or infringing methods from non-infringing methods."[414]

iii. The 'dissenting line'

The other line, followed by a minority of judges of the Federal Circuit, strictly denies a separate written description requirement. The opinions and arguments underlying this "dissenting line" were most clearly articulated in the cases of *Eli Lilly*[415], *Enzo I and II,* and *Rochester*[416]. For the opponents of a separate written description requirement, to make a distinction between the disclosure of how to 'make and use' an invention and a disclosure that shows that an invention has in fact been "possessed" is "contrary to logic and the statue itself." Underpinning the dissenting line

410 Warburg, Richard J./Wellman, Arthur/Buck, Todd/Ligler Schoenhard, Amy E., Patentability and Maximum Protection of Intellectual Property in Proteomics and Genomics, 22 Biotechnology Law Report 2003, 264, 269.
411 University Of Rochester v. G.D. Searle & Co., Inc., 358 F.3d 916, 919.
412 University Of Rochester v. G.D. Searle & Co., Inc., 358 F.3d 916, 920.
413 University Of Rochester v. G.D. Searle & Co., Inc., 358 F.3d 916, 922-923.
414 University Of Rochester v. G.D. Searle & Co., Inc., 358 F.3d 916, 926.
415 Regents of the Univ. of Cal. v.. Eli Lilly & Co., 119 F.3d 1559 (Fed.Cir.1997). The decision was criticized in University of Rochester v. Searle, 375 F.3d 1303, 1307 (Fed. Cir. 2004).
416 University of Rochester v. Searle, 375 F.3d 1303, 1307.

is the view that, Section 112, first paragraph requires that the patent document "enables" the invention in terms of providing information sufficient to allow one with ordinary skill in the art to make and use the invention without undue experimentation. To advocate that the written description serves a purpose over and above the enablement factor leads to the anomaly that a patent specification could apparently enable a skilled artisan to make and practice the entire invention, but still not prove that the inventor possessed the invented subject matter.[417]

Besides arguing that "a straightforward reading of the text of Section 112 suggests that the test for an adequate written description is whether it provides enough written information for others to make and use the invention,[418] Judge Rader cited Federal Circuit precedent. He reasons that the cases[419] established by the Federal Circuit's predecessor concluded that the patent claims as such satisfy the written description requirement. Hence, the specification did not necessarily have to comply with a written description requirement.[420] Moreover, Judge Rader argued that, prior to the *Eli Lilly* decision; the case law had not applied the written description requirement to questions of validity. In contrast, the application of the principle was merely restricted to questions of priority in order to determine the first inventor of the claimed subject matter. The separate written description doctrine, according to Judge Rader's view, created "enormous confusion."[421]

Affirming summary judgment in *Enzo I,* the Federal Circuit extended the reach of *Lilly*. The claims at issue were directed to nucleic acid probes which where specified for bacteria that cause gonorrhea. The patent described the binding affinity of claimed sequences, and deposited three probes that met the claim limitations.[422] The court held that reference in the specification to deposits in public depositories of nucleic acid probes whose sequences were not disclosed in the specification, but which possessed a known functionality, may not satisfy the written description requirement.[423] The court argued that the inventor's disclosure was "purely functional" because the hybridization conditions did not identify the sequences but merely described what they do.[424] Even though not binding for the court,[425] the Judges also

417 Judge Rader, dissenting from denial of en banc review, University of Rochester v. Searle, 375 F.3d 1303, 1307. (Fed. Cir. 2004).

418 Judge Rader, dissenting in Enzo (denial of en banc review), Enzo Biochem Inc. v. GenProbe Inc., 323 F.3d 956, 976 (Fed. Cir. 2002).

419 In re Gay, 50 C.C.P.A. 725, 309 F.2d 769, 772 (C.C.P.A. 1962); In re Smith, 481 F.2d 910, 914 (C.C.P.A. 1973) ("Where the claim is an original claim, the underlying concept of insuring disclosure as of the filing date is satisfied, and the description requirement has likewise been held to be satisfied.").

420 Judge Rader, dissenting from denial of en banc review, University of Rochester v. Searle, 375 F.3d 1303, 1307.

421 Judge Rader, dissenting from denial of en banc review, University of Rochester v. Searle, 375 F.3d 1303, 1308.

422 Id.

423 Enzo Biochem, Inc. v. Gen-Probe, Inc., 285 F.3d 1013 at 1020. (Fed. Cir. 2002) (Enzo I).

424 Id. at 1018.

425 Enzo I, 285 F.3d at 1019.

noted that the functional description failed to meet the written description guidelines established by the USPTO.[426] While conceding that the inventors, unlike those in *Lilly*, had achieved more than "a mere wish or a plant of obtaining the claimed invention"[427], the majority finally held that the absence of sequence information could not be cured by public deposit."[428]

Judge Dyk's dissenting opinion mainly focused on *Lilly*. In an attempt to highlight the wide-ranging implications of this in his view, misguided decision, he stated that *Lilly* "is open to serious question". Emphasizing the potentially unequal treatment of different fields of innovation and the need for a consistent extrapolation of long-held legal practices, he warns that *Lilly* imposes a "unique written description requirement in the field of biotechnology" and departs form the general rule of "possession" of the invention.[429] In addition, he harshly criticized the majority's view that sequence information could not be made public by public deposit, arguing that reference to a deposit "is an ideal way of satisfying the written description requirement."[430]

The *Enzo I* decision was intensively discussed within the legal profession, and raised serious concerns, especially within the biotech community itself.[431] Against this background, the same panel of judges had to reconsider the case.[432] Taking into account the USPTO's Written Description Guidelines, the panel partly vacated its earlier position. The major aspect of the reversed conclusion was that, in some cases and under certain conditions, a description of the function of genetic materials will be sufficient to meet the written description requirement:

> "[T]he PTO has determined that the written description requirement can be met by showing that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics … i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics."[433]

426 Guidelines for Examination of Patent Applications Under 35 U.S.C. 112, Para 1 "Written Description" Requirement, 66 Fed. Reg. 1099 at 1106 (Jan. 5, 2001) ("WD Guidelines").

427 Enzo I at 1018 (quoting Lilly, 119 F.3d at 1566).

428 Enzo I at 1021.

429 Id. at 1025 (dissenting opinion).

430 Id. at 1027 ("The primary purpose of the statutory written description requirement is to provide notice to comptentitors and the public of the scope of the patent claims.")

431 See, e.g., Brief of Amicus Curiae United States at 1 Enzo Biochem, Inc. v. Gen Probe, Inc., 323 F.3d 956 (Fed. Cir. 2002), cited in Judge Rader dissenting from denial of en banc review in University of Rochester v. G.D. Searle & Co., Inc., 375 F.3d 1303 ("That Enzo opinion caused an immediate firestorm").

432 Enzo Biochem, Inc. v. Gen-Prob, Inc., 323 F.3d 956 (Fed. Cir. 2002) (Enzo II).

433 Id. at 964 (citing Guidelines for Examination of Patent Applications Under 35 U.S.C. 112, Para 1 "Written Description" Requirement, 66 Fed. Reg. 1099 at 1106 (Jan. 5, 2001)). Generally, the WD Guidelines are consistent with the Federal Circuit case law, as they require an applicant "permit a person skill in the art to clearly recognize [the] applicant had possession of the claimed invention." 66 Fed. Reg. at 1105. As for nucleotide sequences, however, the Guidelines did not fully embrace the doctrine of a separate written description requirement as it was developed in Lilly.

Based on this more flexible set of principles, the court remanded the case to the district court, which was asked to determine whether the specification provided sufficient information to "demonstrate possession of the generic scope of the claims" by the inventors.[434] Emphasizing the significance of the deposits and the scope of the claims, the remand order entrusted the district court to determine whether the claimed subject matter had been sufficiently disclosed, as judged by a person skilled in the art.[435]

While providing a more flexible interpretation, the court followed its earlier view that the mere possession is not sufficient for a disclosure. Enzo had claimed that it had shown "possession" of the claimed invention sufficient to meet the requirement of § 112 because it had effectively reduced three sequences within the scope of the claims to practice, Rejecting this argument, the court held that possession is merely "ancillary to the statutory mandate". Without additional information, a claim lacks sufficient disclosure.[436]

In stark contrast to *Enzo I*, the *Enzo II* panel rejected the view that a biological deposit referred to in the specification could not be considered part of the disclosure. It explained that:

> "references in the specification to a deposit in a public depository, which makes its contents accessible to the public when it is not otherwise available in written form, constitutes an adequate description of the deposited material sufficient with the written description requirement of § 112 Para 1."[437]

In sum, the Federal Circuit allowed the rehearing of *Enzo I*, but rejected a petition to rehear the appeal *en banc*.[438] In his dissent from this denial, Judge Rader argued that outside the context of resolving priority, no statute or precedent supports an independent written description requirement.[439] Judge Lourie's concurring opinion rejected this criticism, noting that "[n]ew interpretations of old statutes in light of new fact situations occur all the time."[440] In light of the opinion, a strong written description standard will ensure that in exchange for the exclusive right to practice an in-

434 Id. at 966.
435 Id. at 967.
436 Id. at 969.
437 Enzo II, 323 F.3d 965.
438 Id. at 970.
439 Id. at 978 (dissenting opinion) ("The function of the description requirement is to ensure that the inventor had possession, as of the filing date of the application relied on, of the specific subject matter later claimed by him. In sum, WD was a new matter doctrine, a priority policeman.") (citing In re Wertheim, 541 F.2d 257, 262 (C.C.P.A.A 1976). Based on this historical genesis of the written description requirement, Judge Rader condluced that the requirement's sole purpose served the "very clear function [of] preventing new matter from creeping into the claim amendments." Id. Jdge Linn's dissenting opinion raised similar arguments. Id. at 987.
440 Id. at 971.

vention, a patentee must disclose both what the invention is and how to make and use it.[441]

Judge Rader's view is illustrated in his dissenting from denial of *en banc* review in *University of Rochester v. Searle*. For the Judge the fact that the court first "faithfully followed *Eli Lilly*" but later reversed the decision as being invalid means that the *Eli Lilly* description doctrine was misguiding.[442] With regard to the "practical problems" that an application of the *Eli Lilly* position created, Judge Rader concluded:

> "This new 1997 rule changes the established rules of claiming and disclosing inventions. Many biotechnological inventions predate *Eli Lilly*. Before the 1997 change, no inventor could have foreseen that the Federal Circuit would make a new disclosure rule. Without any way to redraft issued patents to accommodate the new rule, many patents in the field of biotechnology face serious and unavoidable validity challenges simply because the patent drafter may not have included the lengthy nucleotide sequences."[443]

Judge Rader further raises fundamental patent policy concerns:

> "Must a University or small biotech company expend scarce resources to produce every potential nucleotide sequence that exhibits their inventive functions? Perhaps more important for overall patent policy, must inventors spend their valuable time and resources fleshing out all the obvious variants of their last invention instead of pursing their next significant advance in the useful arts? Again, *Eli Lilly* and *Rochester* appear to have given little thought to these unintended consequences."[444]

Hence, the Judge is particularly concerned that the described uncertainty may affect pharmaceutical and biotechnological industries, as patent protection has been described as the industries' "lifeblood." Biotechnological drug design necessarily depends on the expenditure of both time and money. Judge Rader further argues that a separate written description requirement extends uncertainty and imposes costs to the judicial system:

> "[A] trial court, as in this case, must first ask its jury whether the specification provides sufficient information to enable one of ordinary skill in the art to make and use the invention. Then the trial court must ask the jury again to look at the same specification for information that an inventor of extraordinary skill "possessed" the invention. … Moreover, the trial court must give separate instructions and entertain separate witnesses on these inseparable patent rules to ensure adequate disclosure. Viewed in the practical terms of trial procedure and jury understanding, this 1997 doctrine unnecessarily complicates and prolongs patent enforcement."[445]

441 Id. at 971-972, 974-975. Judge Newman considered the patent description the "foundation of the patent specification."

442 Judge Rader dissenting from denial of en banc review, University of Rochester v. Searle, 375 F.3d 1303, 1308 (Fed.Cir. 2004).

443 Judge Rader dissenting from denial of en banc review, University of Rochester v. Searle,375 F.3d 1303, 1313 (Fed.Cir. 2004).

444 Judge Rader dissenting from denial of en banc review, University of Rochester v. Searle, 375 F.3d 1303, 1313 (Fed.Cir. 2004).

445 Judge Rader dissenting from denial of en banc review, University of Rochester v. Searle, 375 F.3d 1303, 1314. The judge confirmed his opinion in his dissent from the order denying rehearing en banc in Lizardtech, Inc. v. Earth Resource Mapping, 433 F.3d 1373, 1376 (Fed.

Judge Linn also dissented from the court's decision not to hear the case en banc. He agreed with Judge Rader with regard to the "confusion our precedent in *Eli Lilly* and *Enzo* has engendered in establishing 'written description' as a separate requirement on which a patent may be held invalid." *Eli Lilly*, Judge Linn stated, constituted the first time that the Federal Circuit had done so. According to Linn, the essential question of Section 112, first paragraph is whether the written description describes the invention recited in the claims – themselves part of the specification – in a sense that it is sufficient to enable a person of ordinary skill in the art to make and use the claimed invention and practice the best mode contemplated by the inventor. Hence, Judge Linn argues, *Eli Lilly* "should be overturned". According to his view, a separate written description requirement creates "an inevitable clash between the claims and the written description" as the emphasis of the application. In his eyes, only the claims "establish the bounds of the right to exclude" and "construing Section 112 to contain a separate written description requirement beyond enablement and best mode creates confusion as to where the public and the court should look to determine the scope of the patentee's right to exclude."[446]

Judge Dyk takes a midpoint between the other positions, reasoning that Section 112 contains a separate written description requirement, which applies in the context of priority and validity disputes. However, he cautions his view by stating that his vote should not be taken as an endorsement of our existing written description jurisprudence. According to his view, it is necessary that satisfactory standards be applied to all fields of technology articulated.[447]

The current dispute in the U.S. shows a high level of uncertainty surrounding a major patentability condition. But is the strict emphasis of a separate written description requirement necessary for adequate patent protection? Pursuant to claim constructing rules, the claims are the decisive element for the determination of scope. Thus, a person skilled in the art should be able to define the scope with the help of the claim language and the amendments made in the course of the patent application process. A separate weight of the written description requirement, by contrast, obliges the patent applicant to provide a precise definition of the subject matter claimed in structural terms. If he is not capable of doing so, the claim fails. Such a focus on structural features makes it almost impossible to use functional terminology in the patent claims. The inventor has rather to describe all compositions claimed by their chemical structure. Therefore, the enablement factor should be considered a sufficient means to evaluate whether the inventor does not try to claim beyond the

Cir. 2006) ("This court's written description jurisprudence has become opaque to the point of obscuring other areas of this court's law.").445

446 Judge Linn dissenting from denial of en banc review, University of Rochester v. Searle, 375 F.3d 1303, 1325.

447 Judge Dyk concurring from denial of en banc review, University of Rochester v. Searle, 375 F.3d 1303, 1327.

scope of what he has disclosed. Hence, a separate written description obligation appears unnecessary.[448]

b) Europe (Sufficient disclosure)

The European "sufficient disclosure" requirement is laid down in Articles 83 and 84 EPC, the respective Implementing Regulation as well as in the EPO Guidelines for Examination. Under Art. 83 EPC, a European patent application must disclose the invention in "a manner sufficiently clear and complete for it to be carried out by a person skilled in the art." Art. 84 EPC requires that patent claims are "supported by the description." The Implementing Regulation to the EPC, Rule 42(1)(e) (former Rule 27) states that the inventor is required to "describe in detail at least one way of carrying out the invention claimed." Finally, The EPO Guidelines for Examination[449] determine that the description must disclose sufficient detail to render it apparent to the skilled person how to put the invention into practice without having to perform any undue burden or inventive activity.[450]

Consistent with the diverse nature of biotechnological inventions, there are overly restrictive rules as to how much information has to be provided in a patent application. In principle, even broad claims can be supported by disclosing merely one way of performing the claimed subject matter, provided that the invented effect can be easily achieved by the skilled person. In addition to the example provided, however, the application must contain sufficient information to enable the person skilled in the art to perform the invention over the whole area claimed.[451] In all cases, the amount of technical details to be disclosed is highly context-specific. The more difficult it is to obtain the claimed effect, the more technical features and the more examples have to be provided.

448 A different view is presented in Mull, William C., Using the Written Description Requirement to Limit Broad Patent Scope, Allow Competition, and Encourage Innovation in Biotechnology, 14 Health Matrix: Journal of Law-Medicine 2004, 393-435, 435, concluding that "[t]he Federal Circuitis correctly applying the written description requirements part of the disclosure to limit broad claim scope in biotechnology patents. The written description requirement is separate from the enablement requirement and applies to all claims."

449 Guidelines for Examination in the EPO, Part C-II, 4.9., available at http://www.epo.org/patents/law/legal-texts/guidelines.html, last checked on January 21, 2008.

450 T727/95, Weyerhaeuser Company/Ajinomoto, OJ 2001, 1; Benkard/Schäfers, EPÜ, Art. 83, No. 48.

451 See Guidelines for Examination in the EPO, Part C-II, 4.9., available http://www.epo.org/patents/law/legal-texts/guidelines.html, last checked on January 21, 2008; Benkard/Schäfers, EPÜ, Art. 83, No. 50; T435/91 Reinigungsmittel/UNILEVER, N. Publ., No. of the Reasons 4.1.2, 4.14.

As for biotechnological inventions more narrowly, a number of examination guidelines and implementing regulations are highly relevant.[452] First, if the invention is defined in terms of a parameter, the application must provide a clear description of the methods used to determine the parameter values, unless the skilled person would be knowledgeable with regard to what method to use.[453] Second, the deposit of biological material is regulated by Implementing Regulations to the EPC, Rules 33 and 34 (former Rules 28 and 28a.)[454] The deposit has to be made as of the filing date. This is contrary to U.S. patent law, where the deposit must be made at any time the patent is granted.[455] Third, the EPO, in line with other patent offices worldwide, requires a written and computer-readable sequence protocol for the sufficient disclosure of protein and gene inventions (Implementing Regulations to the EPC, Rule 30(1) (former Rule 27 a)).[456]

Large numbers of cases deal with the interpretation of Art 83 and 84 EPC. In *Polypeptide Expression/Genentech,*[457] the court ruled that an invention the claim on which prohibits from multiple uses can be enabled by disclosing a single use only. The case dealt with a patent application that had been rejected because the terms "plasmid" and "bacteria" were considered too broad, since some of them depended on yet unavailable entities. The Technical Board of Appeals, classifying the critical expressions as functional terms, approved that they were allowable if "such features cannot otherwise be defined more precisely without restricting the scope of the invention and their reduction to practice was not an undue burden".[458] It argued that the inclusion of yet unavailable entities resembled the protocol of using broad 'comprising-language' and had to be seen as "normal practice in many technical

452 Most of the relevant rules were released in a specific protocol, which determines how amino acid-related information should be released. See decision of the President of the EPO dated 02.10.1998 concerning the representation of nucleotide and amino acid sequences in patent applications and the filing of sequence listings, see Suppl. No. 2 to OJ EPO 11/1998, 1-68; Singer/Stauder, EPC, Vol. 1, Nos. 70-75; Meyer-Dulheuer, K.-H., Der Schutzbereich von auf Nucleotid- oder Aminosäurensequenzen gerichteten biotechnologischen Patenten, GRUR 2000, 179, 179.

453 Guidelines for Examination in the EPO, Part C-II, 4.9.

454 Singer/Stauder, EPC – Vol. 1, Nos. 76-101; Schulte/Moufang, PatG mit EPÜ, Nos. 449-516; also Straus, Joseph/Moufang, Rainer, Deposit and release of biological material for the purposes of patent procedure: industrial and tangible property issues, Baden-Baden 1990, 69. The formal deposit requirements correspond to the provisions of the Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure that was signed by almost all member states of the European Patent System. BGBl II 984 II 679 = BIPMZ 84, 318 = TabuDPMA Nr. 635; Schulte/Moufang, PatG mit EPÜ, No. 453; Busse/Keukenschrijver, PatG, § 34, No. 311.

455 See In re Lundak, 227 USPQ 90 (CAFC 1985).

456 See Meyer-Dulheuer, K.-H., Der Schutzbereich von auf Nucleotid- oder Aminosäurensequenzen gerichteten biotechnologischen Patenten, GRUR 2000, 179, 179. The particular amino acid sequence must be determined; it is not sufficient to merely disclose the protein's variant, see Busse/Keukenschrijver, PatG, § 34, No. 271.

457 T 292/85, Polypeptide Expression/Genentech, OJ 1989, 275.

458 T 292/85, Polypeptide Expression/Genentech, OJ 1989, 275, 283.

fields."[459] It is thus sufficient that at least one use is clearly indicated, which enables the skilled person to carry out the invention.[460]

The Technical Board of Appeals has always denied the application of an official "one way rule." Nevertheless, the analysis of their case law reveals that such a rule has been a frequently used practice.[461] For example, the Board in *Harvard* remanded the decision of the opposition division that had limited the patent scope, and decided that the patent granted was confined to rodents and no longer to non-human mammals. The Board held that, on the base of the *Genentech* ruling:

> "The description of the invention firstly ensures that the inventions can be reproduced on mice. And secondly, it may be assumed that the skilled person is aware – in the same way as in case T 0292/85 – of other suitable mammals on which the invention can likewise be successfully performed. There is thus no reason why the application should be refused."[462]

In *Fuel oils/Exxon,*[463]the Technical Board of Appeal narrowed down the potential for an overly broad interpretation of the patent description, by emphasizing that:

> "…the disclosure of one way of performing the invention is only sufficient within the meaning of Article 83 EPC if it allows the person skilled in the art to perform the invention in the whole range that is claimed."[464]

The exact way to interpret "whole range", however, remained undetermined, as the Board made clear that such determination must be made on a case-by-case-basis.[465]

In *ALSTOM Holdings/ABB Patent GmbH*[466], the European Board of Appeals determined that the person skilled in the art must be able to carry out the fundamental aspect of the technical teaching of an invention:[467]

> "[T]he disclosure in a patent application or patent must enable a person skilled in the art to carry out successfully the claimed invention in practice in the *whole range* claimed… [I]t is … of no significance whether the invention could have been carried out in the form of a variant covered by the wording of the claim … if this variant does not correspond to the fundamental aspect of the technical teaching of the invention to which the only concrete embodiment dis-

459 T 292/85, Polypeptide Expression/Genentech, OJ 1989, 275, 284.

460 T 292/85, Polypeptide Expression/Genentech, OJ 1989, 275, 284. In Biogen, the Technical Board approved the ruling of Genentech, stating that "…this provision has previously been interpreted by the Board of Appeal in decision T 292/85 … as being satisfied 'if at least one way is clearly indicated enabling the skilled person to carry out the invention'. In other words, in the Board's view, it is not necessary for the purpose of Article 83 and 100(b) EPC that the disclosure of a patent is adequate to enable the skilled man to carry out all conceivable ways of operating the invention which are embraced by the claims …" See T 0301/87, Biogen, OJ 1990, 325, 343.

461 See Bostyn, Sven J.R., A European Perspective on the Ideal Scope of Protection and the Disclosure Requirement for Biotechnological Inventions in a Harmonized Patent System, 5 The Journal of World Intellectual Property 2002, 1014, 1023-1024.

462 T 19/90, Onco-mouse/Harvard (1990), OJ 1990, 476.

463 T 409/91, Fuel oils/Exxon, OJ 1994, 653.

464 T 409/91, Fuel oils/Exxon, OJ 1994, 653, 660.

465 T 409/91, Fuel oils/Exxon, OJ 1994, 653, 660.

466 T 1173/00, ALSTOM Holdings/ABB Patent GmbH, OJ EPO 2004, 16.

467 T 1173/00, ALSTOM Holdings/ABB Patent GmbH, OJ EPO 2004, 16, 27.

> closed refers… A variant which is clearly not based on the same technical effect is not suitable as a basis for generalizations of this type."[468]

Requiring that the "fundamental aspects of the technical teaching" have to be disclosed, does not imply an additional and separate written description requirement. In *Kirin-Amgen,* a case in which the claim at issue was directed to the recombinant production of Erythropoietin, the Board made clear that broad claims are generally allowed:[469]

> "…it is a fundamental principle of patent law that a claim can validly cover broad subject matter, even though the description of the relevant patent does not enable every method of arriving at the subject matter to be carried out. Otherwise no dominant patent could exist, and each developer of a new method of arriving at the subject matter would be free of earlier patents. In many cases in the field of biotechnology, patent protection would then become illusory."[470]

The Board thus made clear that patentability requirements may not be interpreted in a way that impedes the granting of broad patents.

The decision of *Production of Erythropoietin/Kirin-Amgen, Inc*[471] also exemplifies how limits are set regarding the deposit of biological material. With the mere guidance of the disclosure and without deposit of recombinant host cells, the appellants argued, the enablement of the claimed embodiments was only possible after exerting 4½ years of effort, "which was an unacceptable burden."[472] The appellees argued that "once the Epo gene was cloned and the sequence made available, it was straightforward for someone to clone and express the Epo gene."[473] In response to these arguments, the Board of Appeal stated that Art. 83 EPC only requires a deposit if others were not able to "repeat the invention at all."[474] It also made clear that undue burden could not be a rationale for requiring a deposit:

> "This concept relates more to cases where the route that the reader is to follow is so poorly marked that success is not certain. If the route is certain but long and laborious, the patentee is under no obligation to assist the disclosure by making actual physical samples, e.g. the "factory" available. To come to the opposite conclusion would be effectively to introduce a requirement to make the best mode immediately accessible to the public, and such a requirement is not part of the European patent system."[475]

In *The General Hospital Corporation,*[476] the court made clear that "undue burden" is determined from the perspective of a person skilled in the art. The case is also relevant because it directly refers to the need to disclose information that relates to the

468 T 1173/00, ALSTOM Holdings/ABB Patent GmbH, OJ EPO 2004, 16, 26.
469 Kiren-Amgen/Erythropoietin [2000] E.P.O.R. 135 (EPO 1998). See, more generally Bostyn, Sven J.R., A European Perspective on the Ideal Scope of Protection and the Disclosure Requirement for Biotechnological Inventions in a Harmonized Patent System, 5 The Journal of World Intellectual Property 2002, 1014ff, 1026.
470 Kiren-Amgen/Erythropoietin [2000] E.P.O.R. 135, 145.
471 T 412/93, Production of Erythropoietin/Kirin-Amgen, Inc., [1995] E.P.O.R. 629.
472 T 412/93, Production of Erythropoietin/Kirin-Amgen, Inc., [1995] E.P.O.R. 629, 633.
473 T 412/93, Production of Erythropoietin/Kirin-Amgen, Inc., [1995] E.P.O.R. 629, 638.
474 T 412/93, Production of Erythropoietin/Kirin-Amgen, Inc., [1995] E.P.O.R. 629, 657.
475 T 412/93, Production of Erythropoietin/Kirin-Amgen, Inc., [1995] E.P.O.R. 629, 657.
476 T 497/02, The General Hospital Corporation, N. Publ. (EPO 2004).

secondary and tertiary structure of proteins. The claim was directed to the use of a peptide in the preparation of an agent for the treatment of diabetes mellitus. The Board of Appeal rejected the claim for a lack of sufficient disclosure under Art. 83 EPC, arguing that the patent application did not provide any evidence that the cited peptides were in fact performing the required biological activity. The skilled person therefore has to perform tests and experimentations that amount to an undue burden with no certainty of success. The board explained:

> "… that the biological activity of proteins is highly dependent on their secondary and tertiary structures, resulting from their primary structure… There is no basis in the application to conclude that any of the 31 peptides involved, or, if any, how many thereof will show secondary and tertiary structures, giving them properties that make them candidates for use in the treatment of diabetes mellitus."[477]

To sum up, the European sufficient disclosure requirement is met by adequately enabling practice of the full scope of the claim and disclosing in the specification at least one method. An inventor is required to provide sufficient information to 'make and use' the invention, but not to separately describe every single element of the patented subject matter. Applicants are required to provide the information necessary for a skilled person to carry out the invention in the whole area claimed without any undue experimentation.[478]

Finally, and in contrast to the U.S. situation, it is worth noting that the cases represented above suggest that neither Art. 84 EPC nor Art. 83 EPC are used as a basis for a separate written description doctrine. This understanding is consistent with the principle that the claims, rather than the patent description are the decisive element of patent scope, a principle confirmed by further EPC provisions.[479]

III. Conclusion

The comparison of both patent systems shows that a major distinction remains because the U.S. law does not contain an explicit exclusion of patentability due to ethical concerns. In sum, however, the requirements of both systems are in many ways comparable to each other.[480] The currently discussed reform of the U.S. legal system can be understood as a further step towards harmonization.[481] The analysis in this

477 T 0497/02, The General Hospital Corporation, No. of the Reasons 18.

478 Schulte/Schulte, PatG mit EPÜ, § 34, Nos. 362, 367. It is not sufficient that the invention can be carried out generally, it is rather necessary that the skilled person is able to release the claimed invention into practice, see Busse/Keukenschrijver, PatG, § 34, No. 236.

479 Schulte/Kühnen, PatG mit EPÜ, § 14, No. 12. Terms used within the patent claims must be interpreted in accordance to the skilled person's understanding, Busse/Keukenschrijver, PatG, § 14, No. 66.

480 Kleine, Tatjana/Klingelhöfer, Thomas, Biotechnologie und Patentrecht - Ein aktueller Überblick, GRUR 2003, 1, 10.

481 The National Academies' Board on Science, Technology and Economics and the Federal Trade Commission on modernizing U.S. patent law drafted recommendations that suggest

chapter has shown that the era of "genomics" did not require major changes of the patent law systems. The few cases of significant amendments, e.g., the renewal of Section 103 U.S.C.[482] - out of the dilemma where the inventor of a patentable composition of matter used in a process was unable to receive a process patent for the use of this patentable composition - must be considered as mere simplifications rather than a change of principle. It is, however, not guaranteed that the reasoning specified above is sufficient to handle protein folding structure-related claims. In particular, an increasing number of claims directed to protein structures are related to software. It will be interesting to see whether this sector, which is related to bioinformatics, will draw on principles developed for the patentability of computer-implemented inventions. The below case study will further examine this question.

several amendments related to litigation and validity of patents. The provisions that have been reviewed by the American Intellectual Property Law Association (AIPLA) are likely to make the U.S. patent-related litigation simpler and less expensive for small businesses. The recommendations include preserving a "flexible, unitary, open-ended patent system" to "reinvigorate the non-obviousness standard", to "institute a postgrant open review procedure", to "strengthen the USPTO capabilities", to "shield some research uses of patented inventions from infringement liability", to "limit the subjective elements of patent litigation," and to "harmonize the U.S., European, and Japanese patent examination systems". In addition, the proposals include having a period that allows the challenge of patents within a nine to twelve months period, and a first-to-file system; see DeSanti, Susan S./Cohen, William E./Levine, Gail F./Greene, Hillary J./Bye, Matthew, Wroblewski, Michael et al., To Promote Innovation: The Proper Balance of Competition and Patent Law and Policy, 2003; Merrill, Stephan A./Levin, Richard C., Myers, Mark B., A Patent System for the 21st Century, Washington D.C. 2004; American Intellectual Property Law Center, AIPLA Response to the National Academies Report entitled "A Patent System for the 21st Century", Washington D.C. 2005; as for the legislative process, see Kintisch, Eli, U.S. Patent Reform Begins Long journey Through Congress, 308 Science 2005, 1725. The proposals have been summarized in the Patent Reform Act of 2007 that was introduced on April 18, 2007 in both the House of Representatives and the Senate. As of the writing, it is still pending; see 2008 Patent Reform Update, Fish & Richardson PC, available at http://www.fr.com/news/articledetail.cfm?articleid=490, last checked on on January 21, 2008; see also statement of Jon W. Dudas, Under Secretary of Commerce for Intellectual Property and Director of the United States Patent and Trademark Office before the Committee on the Judiciary United States Senate, see "Patent Reform: The Future of American Innovation" June 6, 2007, available at http://www.uspto.gov/web/offices /com/speeches/2007 jun06.htm, last checked on January 21, 2008.

482 See Chapter 3 A II 4 a.

B. Case study related to protein 3-D-structure related inventions

I. Introductory Remarks

1. Aim of the study

Determining compliance of the statutory requirements for patentability cannot be carried out by applying rules *per se*. A better approach is accomplished on a case-by-case basis. Thus, a case study is used to elucidate the legal principles. The following study is based on examples made available by the Trilateral Project WM4[483], which provides a report on comparative study of protein 3-D structure-related claims. The study initially provides background information and proceeds to illustrate how the European Patent Office (EPO), the Japanese Patent Office (JPO) and the United States Patent and Trademark Office (USPTO) are presently treating protein inventions in terms of patent law.[484] The rules set forth have not been officially adopted, but provide substantial guidelines for legal practitioners that seek patent protection.[485] The author will briefly present the approaches made by the USPTO and the EPO.[486] A further step will then examine the given suggestions in the light of existing patent law regulations. Under those circumstances in which the proposals from the EPO and USPTO lack clarity, the author will further develop the existing ideas and apply classical patent and case law principles that have been used in the field of chemistry and genomics. In summary, the following chapters attempt to document the types of patent claims that could be issued and to whom, and to illustrate differences in the criteria being applied by the USPTO and EPO.

Irrespective of the new techniques that have been developed due to advanced knowledge about protein structures, proteomic inventions have to comply with the same principles that have been applied for classical protein inventions in the past. Where these principles are not sufficient to cope with the challenge of 3-D inventions, further development is needed.

483 This case study is based on examples provided by the Trilateral Project WM4, Comparative studies in new technologies (biotechnology, business methods, etc.), Report on comparative study on protein 3-dimensional (3-D) structure related claims (Nov. 2002) (hereinafter Trilateral 3-D protein structure related claims Comparative Study), available at http://www.trilateral.net/, last checked on January 21, 2008.

484 The study has significant implication for the biotechnology industry, Shimbo, Itsuki/ Nakajima, Rie/Yokoyama, Shigeyuki/Sumikura, Koichi, Patent protection for protein structure analysis, 22 Nature Biotechnology 2004, 109, 109.

485 Vinarov, Sara D., Patent protection for structural genomics-related inventions, Journal of structural and functional genomics 2003, 191, 198.

486 Since it is not the subject matter of this analysis, the Japanese view will not be regarded.

2. Major fields of 3-D protein structure inventions

The number of inventions in the field of proteomics has significantly increased after the disclosure of the human genome. First of all, certainly the improved knowledge in genetics pushed forward the further disclosure of protein structures. Scientists, however, also started to focus intensely on protein research and increased investment. 3-D protein structure inventions play an important role in a number of fields. The following attempts to provide an examination of claims related to protein structural properties *per se*, including an analysis of claims to 3-D structure defined by structural coordinates and claims to protein crystals. The next chapter will then focus on proteomics and bioinformatics, including the assessment of claims to *in-silico* screening methods related to tertiary protein structure and identified compounds. Finally, claims directed to data related to structural features will be examined.[487]

II. Proteomics and protein structural properties *per se*

1. Structure defined by structural coordinates and protein crystals

a) Claims

As a first step, claims directed to the polypeptide *per se* are examined. The first group of cases consists of a claim related to a protein having the structure defined by structural coordinates and of another claim that refers to the crystalline form of a protein. The structure definition is based on NMR spectroscopy. With regard to the claim directed to the crystalline protein structure, one must consider that protein crystallization is only possible with a very low percentage of all existing polypeptides. Particularly, hydrophic, (for example membrane proteins) are not available in crystalline form, and it is generally possible to achieve crystalline forms of only 5 % of proteins.[488] Thus, the advantages of this particular claim do not reduce general difficulties of protein patenting.

The actual claims read as follows:

> Claim 1:
>
> An isolated and purified protein having the structure defined by structural coordinates as shown in a specific figure.

487 A number of articles focuses on the Trilateral Study conducted by the patent offices, see for example Masuoka, Kunihisa, Study on the Ways of Protection of Post-Genome Research Products, IIP Bulletin 2002, 84-95; Vinarov, Sara D., Patent protection for structural genomics-related inventions, Journal of structural and functional genomics 2003, 191-209.

488 Peters, Linde, Postgenomik, http://home.t-online.de/home/linde.peters/intro.htm#postgen0, Part IV, 3.

Claim 2:

A crystalline form of protein P having unit cell dimensions of a=4.0nm, b=7.8nm, and c=11.0nm.

b) Background

The claim description of Claim 1 reports the 3-D structure of protein P, including the coordinates of the amino acid side chains, the source organism for protein P and the molecular weight of protein P. Additionally, it provides experimental data and illustrates that the protein, when active, lowers blood pressure. The structural coordinates were derived from a solution phase protein by NMR at O.2nm resolution. The prior art does not include any references that reveal the 3-D structure of the protein. However, it demonstrates a protein from the same source organism having the same specific function and approximately the same molecular weight.[489] With regard to the claim related to the crystalline protein form, a nucleotide sequence encoding the amino acid sequence of protein P is known in the art. The description explains that the administration of protein P was previously shown to lower blood pressure. The inventor alleged the novel production of a stable crystalline form of protein P. The crystalline form of protein P was inactive. The description provides experimental data of how to synthesize the crystals and demonstrates that the protein, when active, lowers blood pressure. Related prior art methods used in protein P crystallization have all been unsuccessful, so that there existed clear technical difficulty in reproducing the claimed crystalline form of protein P.[490]

c) Solutions proposed by the EPO and the USPTO

Regarding the claim directed to the *isolated and purified protein* (Claim 1), the EPO maintained that the claim would not be directed to a subject matter excluded under Art. 52(2) EPC.[491] The claimed subject matter complies with the requirements of

489 European Patent Office, Japan Patent Office, United States Patent and Trademark Office, Trilateral Project WM4, Comparative Studies in New Technologies (Biotechnology, Business Methods, etc.), Report on Comparative Study on Protein 3-Dimensional (3-D) Structure Related Claims, Vienna 2002, 1-79, 7ff.

490 European Patent Office, Japan Patent Office, United States Patent and Trademark Office, Trilateral Project WM4, Comparative Studies in New Technologies (Biotechnology, Business Methods, etc.), Report on Comparative Study on Protein 3-Dimensional (3-D) Structure Related Claims, Vienna 2002, 9.

491 European Patent Office, Japan Patent Office, United States Patent and Trademark Office, Trilateral Project WM4, Comparative Studies in New Technologies (Biotechnology, Busi-

industrial application, clarity, enablement and support. The claim, however, fails the novelty requirement, since the prior art already contains a protein from the same source organism with approximately the same characteristics. The EPO stresses, however, that novelty and inventive step can be accepted if the applicant provides the evidence of novelty over the prior art protein. The structural data fully defines the protein, including the deducible primary sequence.[492]

As to claim 2, which refers to a *crystalline form* of a protein, the EPO states that the claim is directed to a patentable subject matter according to Art. 52(1) EPC. Additionally, the claimed subject matter complies with the requirements of clarity, enablement and support. The requirements of novelty, inventive step and industrial application are given, since the prior art does not include crystals of protein P and also did not illustrate the synthesis of protein P crystals. The EPO suggested, however, to produce the protein in a stable form. The crystals should be used for determination of the 3 D structure and those atomic coordinates, which are useful in *in silicio* screening methods and rational drug design.[493]

The USPTO maintains that an *isolated and purified protein* (Claim 1) may be considered either a composition of matter or a manufactured product and therefore can be considered as statutory subject matter according to 35 U.S.C. § 101.[494] Assuming that there is no evidence that the asserted utility of lowering blood pressure when administered lacks credibility, the claimed protein has a specific, substantial, and credible utility and thus satisfies the utility requirement of 35 U.S.C. § 101. Based on the information that is provided by the specification, a person of ordinary skill in the art is able to synthesize the claimed protein. With respect to the "how-to-use prong"[495] of the enablement requirement, the claimed isolated and purified protein P must, so ruled the USPTO, be effective in modulating blood pressure without undue experimentation. Under this circumstances, the claimed method complies with the enablement requirement of 35 U.S.C. § 101.

The USPTO further states that the patentee provides sufficient structural information such that one skilled in the art recognizes that the inventor is in possession of the invention as claimed. Thus, the written description requirement is fulfilled.

ness Methods, etc.), Report on Comparative Study on Protein 3-Dimensional (3-D) Structure Related Claims, Vienna 2002, 35.

492 Vinarov, Sara D., Patent protection for structural genomics-related inventions, Journal of structural and functional genomics 2003, 191, 203.

493 European Patent Office, Japan Patent Office, United States Patent and Trademark Office, Trilateral Project WM4, Comparative Studies in New Technologies (Biotechnology, Business Methods, etc.), Report on Comparative Study on Protein 3-Dimensional (3-D) Structure Related Claims, Vienna 2002, 35f.

494 Vinarov, Sara D., Patent protection for structural genomics-related inventions, Journal of structural and functional genomics 2003, 191, 203.

495 "The how-to-use-prong of section 112 incorporates, as a matter of law, the requirement of 35 U.S.C. § 101 that the specification discloses a practical utility for the invention… if the application fails as a matter of fact to satisfy 35 U.S.C. § 101, then the application also fails as a matter of law to enable one of ordinary skill in the art to use the invention under 35 U.S.C. § 112," see In re Ziegler, 992 F.2d 1197, 1200-01, 26 USPQ2d 1600, 1603 (Fed. Cir. 1993).

Moreover, the USPTO applies its general practice to the case. Pursuant to this, the examiner rejects the claims as anticipated by, or alternatively as obvious when compared with the reference under the following circumstances: An inventor claims a synthesis in terms of a property or characteristic. The synthesis existing in the prior art appears to be the same as that of the claimed composition, but the particular property or characteristic was not explicitly disclosed by the reference. The rejection is thus supported by evidence or reasoning supporting the indifference over the reference.

An initial search therefore is limited to a conventional prior art search. The patent examiner does a text search with initial search terms referring to the genus and/or species of organism from which the claimed protein was prepared along with an approximate molecular weight. Evidence of impact on blood pressure associated with any proteins found in this search is also considered. A search for an appropriate protein and nucleic acid is also to be made provided the 3-D structure is sufficient to derive amino acid sequence information.[496]

In the case at issue, the prior art demonstrates a protein originating from the same source organism, having the same specific function and approximately the same molecular weight. Although the prior art does not include the atomic coordinates as claimed, the atomic coordinates are an inherent property or characteristic of the claimed protein in a particular state. Lacking evidence that the state defined by the coordinates represents a form distinguishable from that for the protein present in the prior art, the claim must be rejected according to 35 U.S.C. § 102 as being anticipated by, or alternatively, as obvious when compared with the prior art protein (35 U.S.C. § 103). This situation corresponds to the situation in which a claimed protein is characterized by amino acid sequence, but is otherwise identical to a prior art protein that has yet to be sequenced. The Patentee may overcome the rejection by submitting evidence proving that the prior art protein is not the same as, or an obvious variant of, the protein described in the prior art. [497]

As for the *protein crystal* (Claim 2), the USPTO held that it refers to a composition of matter and is therefore patent-eligible subject matter. Assuming that (1.) it is well established in the art that a crystalline form of a protein can generally be reconstituted in an active form, and (2.) there is no evidence that the utility of lowering blood pressure by administering a reconstituted active form of protein P lacks credibility, the claim form has a specific substantial and credible utility as an intermediate in preparing the active form of Protein P. This result persists, even though the claimed crystalline form of protein P is inactive. As to the enablement require-

496 European Patent Office, Japan Patent Office, United States Patent and Trademark Office, Trilateral Project WM4, Comparative Studies in New Technologies (Biotechnology, Business Methods, etc.), Report on Comparative Study on Protein 3-Dimensional (3-D) Structure Related Claims, Vienna 2002, 65.

497 European Patent Office, Japan Patent Office, United States Patent and Trademark Office, Trilateral Project WM4, Comparative Studies in New Technologies (Biotechnology, Business Methods, etc.), Report on Comparative Study on Protein 3-Dimensional (3-D) Structure Related Claims, Vienna 2002, 64-66.

ment, the specification demonstrates the synthesis of the claimed crystals. With regard to the "how-to-use prong" of the enablement requirement it must be assumed that the claims comply with the utility requirement of 35 U.S.C § 101. Additionally, it is necessary to determine whether one skilled in the art could use the claimed invention without undue experimentation. If one skilled in the art could use the claimed protein crystal to make the active form of protein P and thereafter use protein P to modulate blood pressure without undue experimentation, the claimed method would satisfy the enablement requirement of 35 U.S.C. § 112. Since the structure of protein P is provided, the claim complies with the written description requirement. The novelty requirement is met, since the prior art teaches that a crystal of protein P differs from known forms of protein P. As to obviousness under 35 U.S.C. § 103, there is no prior art reference demonstrating or suggesting a crystal of protein P or related proteins. Although a general desire to obtain the crystal structure of any given protein exists, the methodology of doing so is highly unpredictable and specific to each individual protein. Without this expertise in the art of protein crystallization, the synthesis of a specific known protein in crystalline form is nonobvious.[498]

d) Discussion

As for novelty of the *isolated and purified protein* (Claim 1), the EPO applies principles that have been developed by a German court for the patentability of chemical substances. As established in the *Trioxane* decision of the German Federal Supreme Court[499], a chemical substance can be described sufficiently and unambiguously by different parameters. A parameter existing in prior art is novelty-destroying, if it is specific enough to unambiguously identify a substance. Thus, one must closely examine the value of a given parameter by determining its capacity to individualize a particular substance.[500] If a protein is already unambiguously identified by its primary structure, the creation of novelty due to 3-D structural data is anticipated. The USPTO reaches, on distinct but similar grounds, the same solution.

Prima facie, the patent offices' rejection of Claim 1 might give rise to the notion that the establishment of novelty for proteins defined by structural coordinates will, more generally, face substantive hurdles. To put this impression into perspective (and to shed further light on the novelty requirement in cases in which the prior art includes the primary structure), it is useful to compare Claim 1 with claims in which

498 Vinarov, Sara D., Patent protection for structural genomics-related inventions, Journal of structural and functional genomics 2003, 191-209.

499 BGH, 3 IIC 226 (1972) –Trioxane.

500 Bostyn, Sven J.R., Enabling Biotechnological Inventions in Europe and the United States: A Study of the Patentability of Proteins and DNA Sequences with Special Emphasis on the Disclosure Requirement, Munich 2001, 81.

the three-dimensional structure does play a more prominent role, such as in the case of prion proteins.

As explained earlier[501] the long-held hypothesis that the amino acids in all cases code for a single unique tertiary structure cannot be held anymore. The prion protein (PrP) occurs in two different folding types. The normal, cellular PrP (PrP C) is converted into PrP Sc through a posttranslational process.[502] As detailed in Chapter II, this pathogenic prion form causes neurodegenerative disorders, such as bovine spongiform encephalopathy (BSE), its human equivalent Creutzfeld-Jakob disease (CJD), Kuru and Scrapie. In the case of prions, the 3-D protein structure consequently is a more reliable parameter than the amino acid sequence and must be sufficient to match the novelty requirement. Other neurodegenerative disorders such as Alzheimer's disease or Parkinson's disease are not considered to be prion-based, rather are caused by misfolded 3-D protein structure. Even though the precise molecular structure has not yet been identified, it is already clear that these diseases are accompanied by amyloidal brain plaques.[503] Thus, the 3-D structure can be expected to be the key parameter in these cases as well.[504]

The European Patent Office had not yet dealt with novelty in prions. Cases related to stereochemistry, the study of the 3-D shape of molecules, however, involve similar issues. The major focus of stereochemistry is stereoisomers that are compounds consisting of the same atoms and bonds, but possessing different 3-D structures. The major kinds of stereoisomers are enantiomers, i.e. mirror image stereoisomers, and diastereomers which is simply any stereoisomer that is not an enantiomere.[505]

In T 12/81 the Technical Board of the European Patent office did yet not clearly determine that the spatial form of a stereoisomer suffices to establish novelty, finding that a prior art document anticipated a claim directed to diastereomers, even though it did not specify the exact spatial form of the diastereomers. [506] The Board explained that the prior art document that disclosed a chemical substance described by its structural formula failed to explicitly mention the particular stereospecific

501 See Chapter 1 and Chapter 2 B II 2.

502 Prusiner, Stanley B., Nobel Lecture, 95 PNAS 1998, 13363, 13363.

503 A protein called β-amyloid, discovered in 1984, was found to be the primary component of the brain's plaques. According to the amyloid hypothesis, the build-up of β amyloid causes Alzheimer's disease by destroying brain cells.Travis, John, Saving the Mind Faces High Hurdles, 309 Science 2005, 731, 732

504 Diagnostic methods that rely on 3-D information include 'positron emission tomography' (PET) 'fluorescent staining assay', 'immunoassay' and 'electron microscopic assay', see Masuoka, Kunihisa, Study on the Ways of Protection of Post-Genome Research Products, IIP Bulletin 2002, 84, 89.

505 See Organic Chemistry Online (Published by Paul R. Young), Stereochemistry: Isomerism in Carbon Compounds, available http://www.chem.uic.edu/web1/OCOL-II/WIN/HOME.HTM, last checked January 21, 2008.

506 T 12/81, N. Publ., No. of the Reasons 17. The reaction of the literature on this decision of the Board of Appeals was moderately critical, see Hüni, Albrecht, Zur Neuheit bei chemischen Erzeugnissen in der Spruchpraxis des Europäischen Patentamts, GRUR 1986, 461, 462.

configuration. The Board concluded that nevertheless the document anticipates the particular stereospecific configuration, because the stereospecific configuration must be considered the inevitable result of one of a number of processes adequately described in the prior art document.[507]

The rule that the precise asymmetric form of a stereoisomer must be considered novel in comparison with disclosed racemates is set forth in T296/87.[508] In this case, the Technical Board of the European Patent Office had to decide upon the issue of whether novelty of Enantiomers was anticipated by the description of a racemic mixture, a mixture of equal amounts of left- and right-handed enantionmers.[509] The patent description determined racemates in the state of the art by means of expert interpretation of the structural formula and scientific terms.[510] The problematic issue with regard to novelty was that this did not sufficiently specify the precise configuration of the enantiomers at issue.[511] Due to the asymmetric carbon atom contained in the formula, enantiomers can occur in a plurality of conceivable spatial configurations. With the patent description only determining the racemic mixture, a more specific determination of the spatial enantiomers configuration was lacking. The EPO's Board of Appeal applied the principles developed in the German *Trioxan* decision stating that a chemical substance is held to be new if it is distinguishable from a known substance in an unambiguous parameter.[512] The Board concluded that this configuration is such a parameter. The Board explained that the specific racemates included in the prior art do not alone provide any information related to the configuration in individualized form. Consequently, the description of the racemate mixture bears insufficient information to unambiguously determine enantiomers lacking a reliable parameter.[513]

The principle of that an enantiomer is considered new with regard to a racemic mixture is affirmed and further developed in T 1048/92.[514] Here, the crucial prior art document referred to the enantiomer within an example. Further, it contained a 'Markush formula' that included the exemplified subject. With regard to this Markush formula, it was indicated that the formula includes "various optically active

507 T 12/81, N. Publ.No. of the Reasons 5-17. The Board concluded that "the concept of novelty must not be given such a narrow interpretation that only what has already been described in the same terms is prejudicial to it", see T 12/81, N. Publ., No. of the Reasons 5; also Domeij, Bengt, Pharmaceutical Patents in Europe, Stockholm 2000, 146.

508 T 296/87 Enantionmers/HOECHST, OJ 1990, 195, 206, 207.

509 T 296/87 Enantionmers/HOECHST, OJ 1990, 195, 206. Separating different forms of enantiomers bears significant difficulties, because they have nearly identical properties, see Domeij, Bengt, Pharmaceutical Patents in Europe, Stockholm 2000, 148.

510 "The situation is different if the state of the art includes enantiomers, howsoever designated (D, d, L, l or + or -), which are specifically named and can be produced", see T296/87 Enantionmers/HOECHST, OJ 1990, 195, 207.

511 D- and L-enantiomers

512 T 296/87 Enantionmers/HOECHST, OJ 1990, 195, 206-207.

513 T 296/87 Enantionmers/HOECHST, OJ 1990, 195, 207.

514 T 1048/92, N. Publ. (EPO 1994).

isomers" and that "the invention embraces such optically active isomers".[515] The Board of Appeal held that novelty was established. It reasoned that the applicant had chosen one of the two conceivable configurations of the subjects being exemplified in the prior art document. With regard to the indications concerning the occurrence of optical isomers made in the prior art document, the Board concluded that they did not refer to the individual substance distinguished by its steric form as disclosed by the patent applicant.[516]

With the 3-D protein structure determining the protein's function, it is the most unambiguous parameter. Hence, the tertiary folding type is comparable to the asymmetric configuration of enantiomers. In light of principles developed in the above-described decisions from the field of stereochemistry and in the landmark of *Trioxane*, the tertiary folding structure can suffice to match the novelty requirement.[517] The primary structure of a protein does not always contain sufficient information to unambiguously determine a substance. This is illustrated by the case of prions. The amino acid sequence does not provide sufficient information regarding folding of the prion protein at the tertiary level. The determination of the amino acid sequence lacks important information as to whether a normal, cellular prion (PrP C) or the diseased form (PrP Sc) is given. As a consequence, data related to the folding type of a protein can still establish novelty, even though the amino acid is completely known and publicized. This principle, however, is only applicable to proteins that occur in a plurality of 3-D structures. In cases in which the state of the art teaches that there typically exist only single folding stages, the amino acid sequence must be considered the most reliable parameter. [518]

The USPTO precisely determines with regard to *Claim 1* that a patent applicant must prove that the state defined by the coordinates represents a form distinguishable from that for the protein present in the prior art. The office thus applies its general practice regarding what is considered novel. As stated in *Fiers v. Sugano*, "a precise definition, such as structure, formula, chemical name or physical properties is necessary for providing sufficient identification".[519] This information is provided if the patent applicant offers evidence that the claimed compound is less ambiguous

515 T 1048/92, N. Publ., No. of the Reasons II. A 'Markush formula' is the most concise means of defining a class of chemical compounds in a claim, see T 1020/98, N. Publ., No. of the Reasons 3.1. (EPO 2003).

516 T 1048/92, N. Publ., No. of the Reasons 2.5. See also: Domeij, Bengt, Pharmaceutical Patents in Europe, Stockholm 2000, 149.

517 For the Trioxane decision, see Hirsch, Fritjoff, Neuheit von chemischen Erfindungen, GRUR 1984, 243, 244.

518 As to the applicable principles, see: Rauh, Peter A./Jaenichen, Hans-Rainer, Neuheit und erfinderische Tätigkeit bei Erfindungen, deren Gegenstand Protein oder DNA-Sequenzen sind -- Volker Vossius zum 60. Geburtstag, GRUR 1987, 753, 755; also: Bostyn, Sven, A test too far? A critical analysis of the (non)-patentability of diagnostic methods and consequences for BRCA gene type patents in Europe, Bioscience Law Report 2001/2002, 111-121.

519 Fiers v. Sugano, 984 F. 2d 1164, 1172 (Fed. Cir. 1993).

than what is considered state of the art. Again, numerous U.S. patents granted in the field of stereochemistry are based on this assessment of novelty.[520]

As to *Claim 2* related to a *crystalline form* of a protein, the EPO applies established principles for the patenting of chemical inventions. Generally, chemical substances of the same chemical composition must be considered identical. However, it is not impossible that two substances with the same molecule structure can be viewed as being distinct. They must therefore be distinguishable through reliable parameters. The discrimination of chemical substances of a same chemical composition does not only depend on their form (polymorph) but also on their physical characteristics.[521] As stated in *Trioxan* and stated earlier, the crucial characteristic of a particular chemical compound for determining novelty does not necessarily need to be its chemical constitution. The chemical formula of a chemical substance is rather only one of a variety of existing criteria that can be used for classification.[522] The fact that a chemical formula is generally the most reliable definition of a substance does not mean that other definitions do not exist. It is comparable to the definition of substance based on its physical parameter. There is not just a single method of determining the novelty of a chemical compound, but rather a wide variety of methods.[523]

The EPO's statements regarding other patent requirement can be clearly followed. The solution of the technical problem to establish a crystalline form of protein P clearly involves an inventive step, because it cannot *a priori* be expected that the crystalline protein form consists of any advantages compared to the form that is reported in the prior art. Moreover, it would not have been obvious to a skilled person how to translate protein P into its crystalline form.[524] The claimed crystalline form of protein P is advantageous. The inactive form can be reconstituted into an active form, and administration of the reconstituted active form of protein P is known to result in the reduction of blood pressure. Such characteristics and the knowledge,

520 See for example U.S. Patent 7,211,580: McDonald, Andrew/Bergnes, Gustave/Feng, Bainian/Morgans, Jr., David J./Knight, Steven David/Newlander, Kenneth A./Dhanak, Dashyant/Brook, Christopher A., Compounds, compositions and methods, South San Francisco, CA; Philadelphia, PA 2007.

521 The coherency of polymorphs and particular features is widely known in the field of anorganic chemistry. For example, the polymorphic form of carbon can occur as carbon black, graphite or diamond, the polymorphic form of calcium carbonate as crayon or marble, and the polymorphic form of aluminium oxide in a- and g- modifications. Polymorphic characteristics also exist in organic chemistry. Hirsch, Fritjoff, Die Bedeutung der Beschaffenheit chemischer Stoffe in der Patentrechtssprechung, GRUR 1978, 263, 264; see also Wachenfeld, Joachim, The Patenting of Protein Structures, http://www.vossiusandpartner.com/eng/publication/mip-yearbook.html 2002, Comment.

522 BGH, 3 IIC 226 (1972) – Trioxane.

523 Hirsch, Fritjoff, Die Bedeutung der Beschaffenheit chemischer Stoffe in der Patentrechtssprechung, GRUR 1978, 263, 264; BGH, 3 IIC 226 (1972) – Trioxane.

524 Hirsch, Fritjoff, Die Bedeutung der Beschaffenheit chemischer Stoffe in der Patentrechtssprechung, GRUR 1978, 263, 265.

which this crystalline form provides about the three dimensional structure of protein P allow for the protein's use in drug design.

The USPTO applies *In re Bergstrom*[525] to Claim 2, finding that novelty exists due to the fact that the crystalline form of protein P differs from any known form of protein P. Claims directed to products having distinguishable physical forms comply with the novelty requirement, even where their utility is identical to that of the known product.[526] Consequently, novelty is accepted. With the methodology of obtaining protein crystals being highly unpredictable, it is also consequent that the Office accepts non-obviousness under 35 U.S.C. §103.

2. Protein Domains

As for the second group, the EPO had to examine an invention involving structural protein features as binding pockets and protein domains.[527] A binding pocket or so-called active center of a protein is responsible for the catalytic mode of function. It consists of polypeptides that are specifically folded. Due to the specific concave structure within the enzyme, the active center/binding pocket can bind to a suited substrate. In general, there exist six different types of enzymes, oxidoreductases, transferases, hydrolases, lyases, isomerases and ligases.[528] Of major importance are hydrolases that split a substrate under "hydrolytic" conditions.[529] Hydrolosys refers to the splitting of a chemical compound with adsorption of a water molecule.[530]

A protein domain is a discrete portion of a protein assumed to fold independent of the rest of the protein and possessing its own function. Thus, it is a region of a protein's amino acid sequence that has evolutionary, structural, and functional significance. Pharmaceutical researchers are most interested in protein domains because they determine the "active" or "binding" sites of molecules. The combination of domains in a single protein determines its overall function. Generating a set of structures representative of most of the possible folds for specific protein domains is the basis of interpreting the structures for new proteins based on known fold-structure

525 In re Bergstrom, 427 F. 2d 1394, 1401-1402 (C.C.P.A. 1970).

526 Schering Corp. v. Geneva Pharmaceuticals, 339 F.3d 1373, 1380 (Fed. Cir. 2003)("[T]his court's conclusion on inherent anticipation in this case does not preclude patent protection for metabolites of known drugs."); also In re Cofer, 354 F.2d 664, 666 (C.C.P.A. 1966).

527 European Patent Office, Japan Patent Office, United States Patent and Trademark Office, Trilateral Project WM4, Comparative Studies in New Technologies (Biotechnology, Business Methods, etc.), Report on Comparative Study on Protein 3-Dimensional (3-D) Structure Related Claims, Vienna 2002, 9.

528 Whitford, David, Proteins, Structure and Function, Chichester, West Sussex, U.K. 2005, 191.

529 Whitford, David, Proteins, Structure and Function, Chichester, West Sussex, U.K. 2005, 191.

530 Whitford, David, Proteins, Structure and Function, Chichester, West Sussex, U.K. 2005, 202.

relationships.[531] The particular protein domain shows a significantly higher signaling activity. The transduction of signals at the cellular level refers to the movement of signals from outside the cell to the inside and thus to the question of how membrane receptors transfer information from the environment into the cell's interior. Approximately half of the 25 largest protein families that are encoded by the human genome deal primarily with information processing. Signal movement can be simple. For example, some receptors constitute channels, which, upon ligand interaction, allow signals to be passed in the form of small ion movement either into or out of the cell. These ion movements lead to changes in the electrical potential of the cells that, in turn, propagates the signal along the cell. More complex signal transduction involves the coupling of ligand-receptor interactions to many intracellular events.[532]

a) Claims

The comparative study used the following claims to specify the rules suggested for the patenting of binding pockets and protein domains.

1. An isolated and purified molecule comprising a binding pocket of protein P defined by the structural coordinates of amino acid residues 223, 223, 227, 295, 343, 366, 370, 378 and 384 according to Fig. 1.

2. An isolated and purified polypeptide consisting of a portion of protein P starting at one of amino acids 214 to 218 and ending at one of amino acids 394 to 401 of protein P as set forth in SEQ ID NO: 1.[533]

531 Available at http://www.genomicglossaries.com/content/proteomics.asp., last checked on January 21, 2008. Another arrangement of structural features and functional groups important for biological activity is a pharmacophore. A pharmacophore is an arrangement of structural features and functional groups important for biological activity. Thus, it refers to the atoms that are involved in the binding of a ligand binding pocket as a whole. If, for example, the binding pocket of a protein consists of 30 binding pockets out of which five are involved in the binding of a particular pharmacophore, those five create the pharmacophore of the mentioned ligand. The binding pockets of the protein and of the ligand must fit together. As for pharmaceutical drugs, a pharmacophore is the functionally relevant portion and it assists in determining a protein's entire 3-D structure, see Masuoka, Kunihisa, Study on the Ways of Protection of Post-Genome Research Products, IIP Bulletin 2002, 84-95, 91.

532 Berg, Jeremy M./Tymoczko, John L./Stryer Lubert, , Biochemistry, New York, NY, 2002, 395-424.

533 European Patent Office, Japan Patent Office, United States Patent and Trademark Office, Trilateral Project WM4, Comparative Studies in New Technologies (Biotechnology, Business Methods, etc.), Report on Comparative Study on Protein 3-Dimensional (3-D) Structure Related Claims, Vienna 2002, 9.

b) Background

Protein P is a known protein whose amino acid sequence has been demonstrated. The patent description provided experimental data and explained that the protein lowers blood pressure. The patentees claimed that they had made a novel discovery, specifically that the active residues in the binding pocket of protein P consist of the above mentioned amino acids. The description specified that the possible peptides that begin with any amino acid from position 214 to 218 and end with any amino acid from position 394 to 401 of SEQ ID NO: 1 are protein domains that are able to fold into an active binding pocket of protein P. In addition, the description provided evidence regarding the above mentioned domain. It was explained that the domain showed a significantly higher signaling activity compared to the entire protein P when activated by a natural ligand of protein P. Neither is information available demonstrating the position of the binding pocket of protein P, nor reports suggesting a protein structure domain containing the described binding pocket.[534]

c) Solutions proposed by the EPO and the USPTO

The EPO, firstly, addressed the language of claim 1. The office suggested replacing the word "molecule" by "polypeptide" or compound. If a "molecule" were claimed, the claim would not be sufficiently disclosed, as a molecule as such was not enabled. A claim directed to "polypeptide" would not be directed to any subject matter excluded under Art. 52(2) EPC and comply with the requirements of industrial applicability, clarity, enablement and support.

The EPO rejects Claim 1 on the ground of novelty. Since prior art already includes protein P, the state of the art also comprises the binding pocket. Thus, the natural polypeptide would be prejudicial to the novelty of the claimed subject matter.[535]

With regard to Claim 2, the EPO finds that it is directed to a patentable subject matter according to Art. 52(1) EPC. The requirements of clarity, enablement and support are satisfied. The furnished description would provide sufficient detail regarding the variable ends of the polypeptide. The polypeptide should not be relevant to the blood pressure lowering activity of the claimed portion. The EPO also accepted the novelty, inventive step and industrial application requirements. It states

534 European Patent Office, Japan Patent Office, United States Patent and Trademark Office, Trilateral Project WM4, Comparative Studies in New Technologies (Biotechnology, Business Methods, etc.), Report on Comparative Study on Protein 3-Dimensional (3-D) Structure Related Claims, Vienna 2002, 9.

535 European Patent Office, Japan Patent Office, United States Patent and Trademark Office, Trilateral Project WM4, Comparative Studies in New Technologies (Biotechnology, Business Methods, etc.), Report on Comparative Study on Protein 3-Dimensional (3-D) Structure Related Claims, Vienna 2002, 36.

that the specified portion of protein P was not disclosed in the prior art. Further, there was no demonstration or suggestion that this portion may exhibit a higher signaling activity compared to the complete protein P.[536]

The USPTO stressed that Claims 1 and 2 are patentable, eligible subject matter because they are each directed to a composition of matter (an isolated and purified molecule). Moreover, Claims 1 and 2 meet the utility requirement of 35 U.S.C. § 101 since polypeptides exhibiting the binding pocket as defined in the claim are shown to have a higher signaling activity than protein P when activated by a natural protein P ligand. Further, protein P is known to lower blood pressure when active. Lacking a written description and encompassing a broader scope than is enabled by the specification, Claim 1 is rejected under 35 U.S.C. § 112, first paragraph. The claim does not comply with the written description requirement, because it recites a "molecule" defined only by the "structure" of 9 amino acid residues from a source polypeptide of at least 161 residues. From the view of the USPTO, the recited structure is open-ended and only determines a portion of the claimed molecule. The molecule is defined as a polypeptide, but it might also include residues that are not amino acids or amino acid derivatives. Protein P and the 40 fragments shown to be active all have the naturally occurring amino acid sequence of protein P. They do not constitute a representative number of species of the claimed genus, which include polypeptide and non-polypeptide molecules, to allow one of skill in the art to envision all members of the genus. Therefore, they do not provide an adequate written description of the genus.

As to the enablement requirement, the specification enables the full-length protein P and the specifically disclosed fragment. However, the specification does not enable all molecules encompassed by Claim 1. For the binding pocket to function, the 9 residues must be in the same spatial relationship to each other as they are in the natural polypeptide or the polypeptide fragments disclosed in the specification. The total number of molecules encompassed by the claim is extremely large. This is due to the fact that there are a large number of residues within the pocket that can be changed to comprise any one of 20 amino acids. Additional unspecified moieties may be included on either end of the binding pocket thereby generating a vast number of molecules encompassed by the claim. Further, a lack of guidance exists regarding structural changes, which may be made in the amino acid sequence between and around the active residues in order that the resulting polypeptide retains its 3-D structure and activity at the binding pocket. Therefore, it requires undue experimentation to make and use the invention over the entire scope claimed in Claim 1.[537]

536 European Patent Office, Japan Patent Office, United States Patent and Trademark Office, Trilateral Project WM4, Comparative Studies in New Technologies (Biotechnology, Business Methods, etc.), Report on Comparative Study on Protein 3-Dimensional (3-D) Structure Related Claims, Vienna 2002, 36.

537 European Patent Office, Japan Patent Office, United States Patent and Trademark Office, Trilateral Project WM4, Comparative Studies in New Technologies (Biotechnology, Business Methods, etc.), Report on Comparative Study on Protein 3-Dimensional (3-D) Structure Related Claims, Vienna 2002, 68f.

Claim 2, however, complies with the enablement and written description requirements. It is limited to fragments of protein P that contain the binding pocket described in the specification to retain binding activity and the signaling activity of protein P. The USPTO further stressed that Claim 1 recites open "comprising" language. Thus, the Claim encompasses natural protein P. Claim 1 is anticipated by protein P and therefore lacks novelty according to 35 U.S.C. § 102. Claim 4 is directed explicitly to fragments of protein P consisting of the amino acid residues comprising the binding pocket and retaining binding and signaling activity. These fragments are not included in the prior art and are not rendered obvious based on the known amino acid sequence of the entire protein P.[538]

d) Discussion

Considering the statements provided by the patent offices, it must be noted that the EPO provides only very brief conclusions, whereas the USPTO gives a more detailed description of its reasoning. The two offices adopted similar approaches in their assessment of Claims 1 and 2. They found that the patentable subject matter is easily satisfied. The criteria of description and enablement warranted more analysis. Both the EPO and the USPTO held that Claim 1 referring to a molecule does not satisfy the written description requirement. It is remarkable that the offices do not refer to the enablement factor in the context of comprising language, which they only examine with regard to novelty. The matter of "comprising language" has been the subject of a number of discussions.[539]

The USPTO referred to the character of "open comprising language" with regard to the patenting of DNA fragments (ESTs) in consideration of the "written description guidelines" of January 5, 2001. [540] In Footnote 13 of the official document, the office states:

> "A determination of what the claim as a whole covers may result in a conclusion that specific structures such as a promoter, a coding region, or other elements are included. Although all genes encompassed by this claim share the characteristic of comprising SEQ ID NO: 1, there may be insufficient description of those specific structures (e.g. promoters, enhancers, coding regions, and other regulatory elements) which are also included."

Moreover, the office specified its view in the "Synopsis of Application of Written Description Guidelines"[541]:

538 European Patent Office, Japan Patent Office, United States Patent and Trademark Office, Trilateral Project WM4, Comparative Studies in New Technologies (Biotechnology, Business Methods, etc.), Report on Comparative Study on Protein 3-Dimensional (3-D) Structure Related Claims, Vienna 2002, 69.

539 Krefft, Alexander Richard, Patente auf human-genomische Erfindungen: Rechtslage in Deutschland, Europa und den USA, München 2003, 281.

540 Guidelines for Examination of Patent Applications under the 35 U.S.C. 112, P1, "Written Description" Requirement, 66 FR 1099 (January 5, 2001).

541 Synopsis of Application of Written Description Guidelines, available at

> "In the case of a partial cDNA sequence that is claimed with open language (comprising), the genus of, e.g., "A cDNA comprising [a partial sequence]," encompasses a variety of subgenera with widely varying attributes. For example, a cDNA's principle attribute would include its coding region. A partial cDNA that did not include a disclosure of any open reading frame (ORF) of which it would be a part, would not be representative of the genus of cDNAs because no information regarding the coding capacity of any cDNA molecule would be disclosed. Further, defining "the" cDNA in functional terms would not suffice in the absence of a disclosure of structural features or elements of a cDNA that would encode a protein having a stated function. (…)"[542]

In the course of the Synopsis, the USPTO referred to a specific claim which was rejected due to its comprising language. The USPTO in this case argued the following:

> "Here, the specification discloses only a single common structural feature shared by members of the claimed genus, i.e., SEQ ID NO: 16. Since the claimed genus encompasses genes yet to be discovered, DNA constructs that encode fusion proteins, etc., the disclosed structural feature does not "constitute a substantial portion" of the claimed genus. Therefore, the disclosure of SEQ ID NO: 16 does not provide an adequate description of the claimed genus. Weighing all factors, 1) partial structure of the DNAs that comprise SEQ ID NO: 16, 2) the breadth of the claim as reading on genes yet to be discovered in addition to numerous fusion constructs and cDNAs, 3) the lack of correlation between the structure and the function of the genes and/or fusion constructs; in view of the level of knowledge and skill in the art, one skilled in the art would not recognize from the disclosure that the applicant was in possession of the genus of DNAs which comprise SEQ ID NO: 16. Conclusion: The written description requirement is not satisfied."[543]

Accordingly, the USPTO in the case of the synopsis rejected the DNA claim on the basis that the comprising language is too broad for sufficient enablement. The arguments outlined in the above cited example, however, do not equally apply to the proteomic case at issue. As to the synopsis, the USPTO alleges that the breadth of claim regarding genes yet to be discovered in addition to numerous fusion constructs and cDNAs leads to a lack of enablement. The case at issue, by contrast, involves a protein (P) that is already included in the prior art and thus disclosed. The breath of claim consequently only refers to features that are already state of the art. Thus, the use of comprising language does not lead to a lack of enablement. The term "comprise" is not rejected as failing the enablement factor in general, but only in the case where sufficient enablement is not provided by the given written description and/or by the prior art. This differentiated view of the phrase "comprise" complies with former statements provided by both patent offices. In the Trilateral report considering the patenting of ESTs, the USPTO stated that "comprising claim" indeed would

http://www.uspto.gov/web/menu/written.pdf, p. 31-32, last checked on January 21, 2008.

542 In this context the USPTO referred to the claim formulation of Regents of the University of California v. Eli Lilly & Co., 119 F3-D 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). Here, a description of a genus of cDNAs had been achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus.

543 "Synopsis of Application of Written Description Guidelines available at: http://www.uspto.gov. /web/menu/written.pdf, 31, last checked on January 21, 2008.

be broader than the "consisting claim".[544] The crucial question, however, would be whether the invention could be carried out in light of the *In re Wands* factors, which serve to assess sufficient enablement. [545]

In *Ak Steel Corp. v. Sollac*, the Federal Circuit extensively commented on the interpretation of "comprising" and "consisting", holding that a "comprising claim" must be considered as "open-ended".[546] Accordingly, the court does generally accept "comprising language" under the written description requirement. The question of sufficient enablement rather has to be assessed by the analyses of the *In re Wands* factors and does not primarily depend on the question of what is included from a comprising claim. Moreover, the question must be decided on the grounds of each given case.[547]

The EPO also considered the interpretation of the terms "comprising"/ "consisting" on various occasions, that collectively mirror a differentiated approach. In the course of the Trilateral Project related to the patenting of DNA fragments the offices held that

> "We are not able to see any difference when judging invention activity with respect to the claim language "consisting of" or "comprising". [548]

As to the particular "comprising claim" directed to ESTs the office states that it does not include DNA with unlimited length, but rather lengths that are still suitable for the purpose of DNA micro array technologies. In T 759/91, the Board of Appeal of the EPO had already extensively analyzed the issue stating that

> "While in everyday language the word "comprise" may have both the meaning "include", "contain" or "comprehend" and "consist of", in drafting patent claims legal certainty normally requires it to be interpreted by the broader meaning "include", "contain" or "comprehend".[549]

Applying the principles set forth above to the claim at issues, it appears consequent that both offices reject claim one. The office applies its well established practice that a claim should only encompass as much as is contained in the description. Here, the description provides information exclusively regarding the polypeptide chain of the

544 Trilateral Project B3b Comparative study on biotechnology patent practices, Theme: Patentability of DNA fragments, available at: http://www.european-patent-office.org/tws/sr-3-b3b.htm.

545 In re Wands, 858 F.2d 731, 731 (Fed. Cir. 1988). (The enablement requirement must be determined in light of "a. The quantity of experimentation necessary to practice the claimed invention; b. The amount of direction or guidance presented in the specification; c. The presence or absence of working examples in the specification; " d. The nature of the invention; e. The state of the prior art; f. The relative skill of those of ordinary skill in the art; g. The predictability or unpredictability of the art; and; h. The breadth of the claims).

546 Ak Steel Corp. v. Sollac, 344 F.3d 1234, 1239, 1244-1245 (Fed. Cir. 2003). The court further explains that the phrase "consisting essentially of" in a patent claim represents a middle ground between the open-ended term "comprising" and the closed ended phrase "consisting of".

547 Ak Steel Corp. v. Sollac, 344 F.3d 1234, 1244-1245.

548 Ak Steel Corp. v. Sollac, 344 F.3d 1234, 1244-1245.

549 T 759/91, N. Publ., No. of the Reasons 2.2. (EPO 1993). See also T 711/90, N. Publ., No. of the Reasons 2.2. (EPO 1993).

protein. Yet, the entire molecule contains additional information not supported by the disclosed description. Therefore, the USPTO consequently applies its written description guidelines, stating that:

> "The claimed invention as a whole may not be adequately described if the claims require an essential or critical feature which is not adequately described in the specification and which is not conventional in the art or known to one of ordinary skill in the art"[550]

It is also consequent that the two offices discuss the comprising language with regard to novelty. They both found that claim 1 does not satisfy the novelty requirement, whereas they concur that the novelty of Claim 2 is established. Notwithstanding the details provided by the USPTO, it is unclear as to how novelty of Claim 2 is derived. The EPO rejects the novelty of Claim 1 on the grounds of that the prior art already reported protein P, meaning that the state of the art also encompasses the binding pocket. Hence, the natural polypeptide is prejudicial to the novelty of the claimed subject matter.[551] The EPO found the novelty of Claim 2 to be given, stating that the prior art did not disclose the specified portion of protein P. The state of the art does not suggests this portion to exhibit an unexpected elevated signaling activity compared to the whole protein P.[552]The USPTO further stresses that Claim 1 is anticipated by protein P and therefore lacks novelty. Due to its open "comprising" language, the claim encompasses natural protein P. The office accepts the novelty of Claim 2 by reasoning that it is directed only to fragments of protein P that were not included in the prior art or were obvious. Hence, the "comprising language" does not only result in a lack of written description, but also in a lack of novelty. With "comprising" being understood in a broader sense than "consisting", Claim 1 encompasses the entire protein P, meaning that it overlaps with what is included in the prior art. According to the Board of Appeal of the EPO, such "overlapping claims" do not focus sufficiently on the specific part of the selection invention.[553] If a skilled person, however, is able to carry out the invention according to the description of the prior art that is used for the support of the new invention, the patent application does not match the standards of a selection invention. Therefore, Claim 1 fails to meet the novelty requirement. In accordance with statements of the patent offices set forth above, only the novelty of Claim 2 can be acknowledged.

550 Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, P1, "Written Description" Requirement, 66 FR 1099 (January 5, 2001).

551 European Patent Office, Japan Patent Office, United States Patent and Trademark Office, Trilateral Project WM4, Comparative Studies in New Technologies (Biotechnology, Business Methods, etc.), Report on Comparative Study on Protein 3-Dimensional (3-D) Structure Related Claims, Vienna 2002, 36.

552 European Patent Office, Japan Patent Office, United States Patent and Trademark Office, Trilateral Project WM4, Comparative Studies in New Technologies (Biotechnology, Business Methods, etc.), Report on Comparative Study on Protein 3-Dimensional (3-D) Structure Related Claims, Vienna 2002, 36.

553 T 279/89, N. Publ., 4.2 (EPO 1991), see also T 279/89, N. Publ., 4.2 (EPO 1991); T 666/89, OJ 1993, 495; T 255/91, OJ EPO 1993, 318; Blumer, Fritz, Formulierung und Änderung der Patentansprüche im europäischen Patentrecht, München 1998, 358.

Could novelty be established, assuming that the claim used "consisting language" instead of "comprising language"? Novelty might be derived under the principles of the first and second medical indication pursuant to Art. 54(5) EPC. As mentioned in Chapter III, a case of a first medical use exists if the invention resides in the initial discovery that a certain substance can be used for medical treatment. In this event, a broad claim to a pharmaceutical composition containing the substance is allowed without restriction of the actually identified medical use. When a further medical use of a substance already known to be pharmaceutical useful is identified, the EPO allows so-called 'second medical use' claims in the Swiss-type format.[554] These claims relate to a new use of an already known substance. Although the principles of first and second medical indication are applicable to field of proteomics, the claim at issue does not meet the requirements of Art. 54(5) EPC. Lacking Swiss-type format, it is not directed to a further use of protein P. The claims merely refer to a new characteristic of protein P and thus cannot be considered novel under the principles of first and second medical indications.

Novelty might further exist under the principles developed for 'selection inventions.'[555] A selection invention refers to an invention in which the constituting elements are derived from the species conception of a generic invention.[556] Specifically, the compound as such has been reported by the prior art, but the more selective structure/pure form etc., remains undisclosed as it falls within the classification of the already known protein.[557] Accordingly, a selection invention refers to technical contents that are not explicitly disclosed by the generic invention.[558] In *Thiochchloroformates/HOECHST* that refers to a process of preparation of a chemical compound, the Board determined that a selection invention exists:

554 Busse/Keukenschrijver, PatG, § 5 No. 33; § 3 No. 201.

555 Guidelines for Examination in the EPO, Part C-IV, 911a explain that "the subject-matter of selection inventions differs from the closest prior art in that it represents selected sub-sets or sub-ranges. If this selection is connected to a particular technical effect, and if no hints leading the skilled person to the selection exist, then an inventive step is accepted (this technical effect occurring within the selected range may also be the same effect as attained with the broader known range, but to an unexpected degree). The criterion of 'seriously contemplating' mentioned in connection with the test for novelty of overlapping ranges should not be confused with the assessment of inventive step. For inventive step, it has to be considered whether the skilled person would have made the selection or would have chosen the overlapping range in the hope of solving the underlying technical problem or in expectation of some improvement or advantage. If the answer is negative, then the claimed matter involves an inventive step." See also Cornish, William/Llewelyn, David, Intellectual Property: Patents, Copyright, Trade Marks and Allied Rights, 6th ed., London 2007, 194.

556 See T 0012/90, N. Publ., No. of the Reasons 3.3.1 (EPO 1990); the patentee claimed novelty on the ground of selective group of chemical compounds. The board rejected, considering the selection as being too broad.

557 Blumer, Fritz, Formulierung und Änderung der Patentansprüche im europäischen Patentrecht, München 1998, 345.

558 Turrini, Enrico, The Concept of Novelty – A Review of the Case Law of the Board of Appeal of the European Patent Office, 22 IIC 932, 938 (1991).

> "if the sub-range selected is narrow ... and sufficiently far removed from the known range illustrated by means of examples. The sub-range is novel not by virtue of an effect which occurs only within it; but this effect permits the inference that what is involved is not an arbitrarily chosen specimen from the prior art but another invention (purposive selection)."[559]

In other words, a) the selected sub-field is required to be narrow, b) the selected field is sufficiently far removed from the known range illustrated by working examples, c) the sub-field must not merely be randomly selected, but should be the result of a more tightly focused technical teaching and d) the selected area should not provide a mere embodiment of the prior art description, but another invention.[560]

These principles developed by the Board of Appeal of the European Patent Office for the field of chemistry[561] are also applicable to protein-related inventions. Like a chemical compound, a protein consists of distinct structural features, which can be compared to a variety of structural items. The composition of those structural items can be considered as being similar to the composition of chemical features. With regard to the claim at issue, the binding pocket/protein domain of Claims 1 and 2 are a narrow field of the disclosed protein P. Being excluded from any working examples known in the prior art, a) and b) are thus satisfied. The focus on the binding pocket structure is intensive and results in a specific selection, and thus complies with c). Consequently, the claim at issue meets the novelty requirement under the principles for selection inventions. Moreover, the involvement of an inventive step is required.[562] With respect to the selection invention a person skilled in the art should not be allowed to complete the technical problem.The selection invention[563] that is deemed to be nonobvious involves an outstanding effect, property, or use when compared with the compounds in the known generic invention.[564] It has been determined that the binding pocket exhibits higher signaling activity which can be defined as an outstanding effect. As to what has been included in the prior art, the elevated signaling activity must be considered an unexpected result and thus can be de-

559 T198/84 Thiochchloroformates/HOECHST, OJ 1985, 209.

560 Blumer, Fritz, Formulierung und Änderung der Patentansprüche im europäischen Patentrecht, München 1998, 345; T 279/89, N. Publ.; see also Domeij, Bengt, Pharmaceutical Patents in Europe, Stockholm 2000, 157-168, 164.

561 Further decisions of the Board of Appeals related to selection inventions are T247/91, N. Publ.(EPO 1982); T45/91, N.Publ. (EPO 1992); T198/84, OJ 1985, 209; T133/92, N. Publ.(EPO 1994). As for the German case law, see Hirsch, Fritjoff, Neuheit von chemischen Erfindungen, GRUR 1984, 243, 245 and the cited decisions therein.

562 Blumer, Fritz, Formulierung und Änderung der Patentansprüche im europäischen Patentrecht, München 1998, 348.

563 The principles of the selection invention thus do not fit under the typical "three-step-examination" of state of the art, novelty and inventive step. Since novelty already depends on the inventiveness, the third step, the "inventive step"m is inherent in the novelty analyses, see Blumer, Fritz, Formulierung und Änderung der Patentansprüche im europäischen Patentrecht, München 1998, 348.

564 Blumer, Fritz, Formulierung und Änderung der Patentansprüche im europäischen Patentrecht, München 1998, 358.

fined as being nonobvious. Consequently, both claims meet the inventive step requirement.

The U.S. patent law system is also familiar with the principles related to selection inventions.[565] The taken approach resembles the European one. A "selection invention" refers to a species or subgeneric invention directed to a prior art reference (i) possessing novelty over the closest disclosed embodiment of that prior art reference; and (ii) being within the scope of that prior art reference. As under European patent law, the crucial element is the distance of the closest embodiment to the claimed inventions. The major question is whether that closest embodiment raises a *prima facie* case of obviousness.[566] The chemical case law is split in this respect.[567] *In re Susi,* the court found a chemical invention to be *prima facie* obvious where the broad prior art disclosure includes at least some of the compounds claimed by the applicant, and the prior art chemicals were of a class to be used for the same purpose as the compounds of the applicant.[568] Thus, any disclosure that includes the chemical materials claimed by the applicant would render the claimed materials obvious and require an applicant to rebut the *prima facie* case with evidence of nonobviousness.[569] The rational established in *Susi* was followed by several other decisions. In *Merck & Co. v. Biocraft Laboratories Inc.,* the applicant claimed solely one of 1200 embodiments disclosed by the prior art.[570] The court found that when the prior art teaches the skilled person that any of the 1200 embodiments could be used; a case of *prima facie* exists. The court held that this was especially true, because the claimed composition was used for the same purpose taught by the prior art.[571] A different line of determining obviousness was set forth with the decision of *In re*

565 A number of further decisions related to selection inventions are cited by Wegner, Harold, Patent Law in Biotechnology chemicals & Pharmaceuticals, New York 1994, 161 and 167. See also In re Petering, 301 F.2d 676, 133 USPQ 275 (C.C.P.A.), indicating that a prior genus could be an anticipation of alter species or Kalman v. Komberly Clark Corp., 713 F.2d 760, 771, 218 USPQ 781, 789. More recently, the CAFC decided in CFMT, Inc. v. Yieldup International Corp. 349 F.3d 1333 (Fed. Cir. 2003) that additional inventive work does not alone show enablement. Developments related to selection inventions do not cast doubt on enablement of the original invention, see also Eli Lilly v. Zenith Goldline, 364 F.Supp.2d 820 (S.D.Ind. 2005) ("Inventions based on the identification or selection of a specific material or compound with particularly desirable properties within a previously disclosed genus of such materials or compounds do not violate any of the substantive requirements for patentability").

566 Wegner, Harold, Patent Law in Biotechnology Chemicals & Pharmaceuticals, New York 1994, 160-161.

567 The principle that it is allowed to claim a narrow range within a broad range disclosed by the prior art is also referred to as "the doctrine of selection inventions", see Varma, Anita/Abraham, David, DNA is different: legal obviousness and the balance between biotech inventors and the market, Harvard Journal of Law & Technology 1996, 53, 69.

568 In re Susi, 440 F.2d 442 (C.C.P.A. 1971).

569 In re Susi, 440 F.2d 442, 446.

570 Merck & Co. v. Biocraft Laboratories Inc., 874 F.2d 804 (Fed. Cir. 1989), cert. denied, 493 U.S. 975 (1989).

571 Merck & Co. v. Biocraft Laboratories Inc., 874 F.2d 804, 807.

Jones.[572] The Federal Circuit held that a *prima facie* obviousness based on structural similarity was not raised where the claimed chemical compound was a subspecies of a broad genus. The court concluded that "we decline to extract from *Merck* the rule that … regardless of how broad, a disclosure of a chemical genus renders obvious any species that happens to fall within it." The court distinguished *Merck* by stating that the claimed species was not specifically disclosed, but merely encompassed by the broad and general prior art teaching. This rational was approved and further developed by *In re Baird*.[573] The applicant's claim involving a bisphenol A[574] had been rejected as being *prima facie* obvious over prior art disclosure of a broad genus of diphenols.[575] The court accepted the claim, stating that there was nothing in the prior art suggesting that a skilled person should select bisphenol A from among more than 100 million diphenols included in the broad genus disclosed in the prior art. The court explained that "[a] disclosure of millions of compounds does not render obvious a claim to three compounds, particularly when that disclosure indicates a preference leading away from the claimed compounds."[576] Finally, in *In re Bell*, the Federal Circuit addressed of what is understood as an inordinately large number of possibilities that faces one skilled in the art attempting to arrive at the claimed DNA sequence.[577] The Court followed the rational set forth in *re Jones*, stating that a *prima facie* case of obviousness requiring a person skilled in the art to select among a large number of choices is not properly decided.[578]

Although the cited case law is not unambiguous, the breadth of claims must be considered the crucial factor with regard to the obviousness requirement. As for the claim at issue, it follows that the claim meets the requirements of novelty and non-obviousness, provided that the patent applicant uses "consisting language" instead of open "comprising language".

572 In re Jones, 958 F.2d 347 (Fed. Cir. 1992).
573 In re Baird, 16 F.3d 380 (Fed. Cir. 1994).
574 Bisphenol A is a chemical substance (phenol) that is used to make polycarbonate plastic.
575 Phenols represents a group of chemical compounds consisting of a hydroxyl group (-OH) linked to an aromatic hydrocarbon group; such as phenol (C6H5OH).
576 In re Baird, 16 F.3d 380, 382.
577 In re Bell, 991 F.2d 781 (Fed. Cir. 1993).
578 In re Bell, 991 F.2d 781, 784; see also Varma, Anita/Abraham, David, DNA is different: legal obviousness and the balance between biotech inventors and the market, Harvard Journal of Law & Technology 1996, 53, 73, and cited case law. The authors also provide a detailed discussion of the In re Bell decision.

III. Proteomics and Bioinformatics

The following claims concern proteomic technologies involving *in-silico* screening methods and the identified compounds thereof, as well as inventions involving the 3-D structural data of proteins *per se.* All these inventions are part of the rapidly evolving area of bioinformatics. *In-silico* screening consists of computerized simulations of the three-dimensional structure of a given polypeptide and was already introduced in Chapter II. The current availability of new information technologies enables scientists to compare a gross amounts of structural data. Therefore, approaches such as *in-silico* screening are increasingly replacing earlier *in-vivo*[579] and *in-vitro* methods.

The major goal of *in-silico* methods is to identify compounds which can bind to a computerized protein. In addition to applications for new *methods*, patent offices are confronted with an increasing number of patent applications related to the *results* from *in-silicio* screening. Specifically, we have seen in recent years the filing of applications involving the identification of candidate compounds which would theoretically form the most stable complex with the computerized 3-D models of proteins. The latter, again, are the subject of an increasing number of applications filed in recent years. Through methods such as NMR structure determination, X-ray crystallography and protein homologous-comparison, the speed of 3-D structure identification has increased steadily. Claims are often directly directed to *in-silicio* screening methods, since applications argue that the findings they put forth are a necessary precondition for compound identification.

Combined with a number of other influences, these new forms of research have resulted in the development of bioinformatics. Bioinformatics, in turn, refers to 'the application of quantitative analytical techniques to the modeling of biological systems'.[580] More specifically, the term describes the development and employment of computer-implemented algorithms and data processing methods directed to data analysis and interpretation.[581] The latter are then used in the design of new pharma-

579 Within a living organism or body. For example testing conducted on whole animals, such as mice.

580 Vorndran, Charles/Florence, Robert L., Bioinformatics: Patenting the Bridge between Information Technology and the Life Science, 93 IDEA - The Journal of Law and Technology 2003, 93-131, 94. Bioinformatics draws researchers from the fields of biology, computer science, statistical mathematics, and linguistics.

581 Rimmer, Matthew, Beyond Blue Gene: Intellectual Property and Bioinformatics, 34 IIC 31, 31 (2003) defines "bioinformatics" as "the art and science of using computer systems to store, manage and analyse biological information that brings together the diverse disciplines of mathematics, statistics, engineering, and computer science to map and model genes and proteins". The purpose of bioinformatics changes in relation to the improved organization of vast amounts and numerous types of biological information, and the clarification of the biological or medical significance of such information through its analyses. See also Masuoka, Kunihisa, Study on the Ways of Protection of Post-Genome Research Products, IIP Bulletin 2002, 84, 85.

ceuticals.[582] The area of bioinformatics has not only attracted a large amount of venture capital in recent years.[583] It also poses a number of fascinating questions in the area of intellectual property rights protection. Among other things, it is closely related to the hotly debated issue of software implemented inventions, which has even been subject of an initiative of the European Commission.[584]

1. In-silico screening methods

One field which the patent offices had to consider were claims related to *in-silico* screening methods. As explained earlier, *in-silico* methods are computerized ways of searching for compounds, using the protein three-dimensional structural data regarding protein active sites.[585] The selection of compounds is achieved by evaluating their desirability in a computational model based on mathematical methods.[586] The method of *in-silico* screening therefore illustrates the major importance computerized techniques have for proteomic inventions. An increasing number of scientific studies are being carried out through the use of computers, a development that has come to be known as "*in-silico* biology".[587]

582 Krefft, Alexander Richard, Patente auf human-genomische Erfindungen: Rechtslage in Deutschland, Europa und den USA, München 2003, 35, who notes that bioinformatics is one of the most promising sectors of genomics. In particular, the ability to simulate entire cells in-silico ('e-cell simulation') is likely to have a large impact on life science in general. Against this background, the Human Genome Project can be understood as yet the greatest achievement of bioinformatics. Fernandez, Dennis/Chow, Mary, Intellectual Property Strategy in Bioinformatics and Biochips, Journal of Patent and Trademark Office Society, June 2003, 465, 465, provide another definition, stating that bioinformatics is understood as "the convergence of analytical and computational tools with the discipline of biological research".

583 The rapid growth of bioinformatics has created an environment of rigorous competitive efforts to create proprietary positions in areas of commercial interest. In the U.S., this development motivated increasing filings of patent applications for bioinformatics-based inventions. In 1999 alone, 289,448 such applications have been filed in the USPTO; see Hultquist, Steven J./Robert Harrison, and Yongzhi Yang, Patenting Bioinformatic Inventions: Emerging Trends in the United States, 20 Nature Biotechnology 2002, 743, 743.

584 Proposal for a Directive of the European Parlament and of the Council on the patentability of computer-implemented inventions, COM(2002) 92 final of 20.2.2002. See also Chapter 3 B III 1 a cc i.

585 Chapter 2 E III 4.

586 Camebridge Healthtech Institute, in-silico & molecular modeling glossary available at: http://www.genomicglossaries.com/content/ molecular _modeling_gloss.asp, last checked on January 21, 2008.

587 Vorndran, Charles/Florence, Robert L., Bioinformatics: Patenting the Bridge between Information Technology and the Life Science, 93 IDEA - The Journal of Law and Technology 2003, 93, 127 stresses that scientists already possessing the requisite computational ability are at a significant advantage, since they are able to accomplish the demands of various industries.

a) Claim 1

Claim 1 of the set of claims considered in this context reads:

> A method of identifying compounds that can bind to a protein P, comprising the steps of:
>
> a) The application of a 3-dimensional molecular modeling algorithm to the atomic coordinates of protein P to determine the spatial coordinates of the binding pocket of protein P.
>
> b) The electronic screening of the stored spatial coordinates of a set of candidate compounds against the spatial coordinates of the protein P binding pocket with the goal of identifying compounds that can bind to protein P.[588]

aa) Background

Protein P was a known protein whose amino acid sequence was also established. The description indicated that the activity of protein P was known to result in lowering blood pressure. It provided the atomic coordinates of protein P, but did not include the position of its binding pocket. Instead, the specification provided general information on programs predicting the binding pocket of proteins and general information commonly used for in-silico screening programs. Prior art had demonstrated methods of peptide modeling and binding using rational drug design, but there was a clear technical difficulty in obtaining the claimed atomic coordinates of protein P. It was assumed in the specification that by using the binding pocket prediction program and *in-silico* screening program, the person skilled in the art could identify compounds binding to the given protein. The description provided no working examples of identifying compounds using the atomic coordinates of protein P. The specification contemplated that by using the binding pocket prediction program and *in-silico* screening program, the person skilled in the art could identify compounds binding to the given protein. The prior art did not include 3-D coordinates of protein P. It did not teach computer programs for prediction of the binding pocket of proteins. Several *in-silico* screening programs referring to predicted binding pockets of proteins are already established.[589]

588 European Patent Office, Japan Patent Office, United States Patent and Trademark Office, Trilateral Project WM4, Comparative Studies in New Technologies (Biotechnology, Business Methods, etc.), Report on Comparative Study on Protein 3-Dimensional (3-D) Structure Related Claims, Vienna 2002, 10.

589 European Patent Office, Japan Patent Office, United States Patent and Trademark Office, Trilateral Project WM4, Comparative Studies in New Technologies (Biotechnology, Business Methods, etc.), Report on Comparative Study on Protein 3-Dimensional (3-D) Structure Related Claims, Vienna 2002, 10.

bb) Patent Offices Analysis

The EPO concludes the *in-silico* claim to be a patentable invention under Art. 52(2) and 52(3) EPC, since it is directed to a method linked to a technical contribution through the use of technical data. Absent any working examples, however, the claimed method does not disclose sufficient information to comply with the disclosure and enablement requirements. The patentee only offers the filing of further technical information in the future. Presently, he does not provide sufficient evidence to ensure a correct prediction of binding-pockets positions.[590]

The USPTO considers the claims to constitute a patentable subject matter, referring to the *'State Street rationale*'.[591] In *State Street*, the court reasoned that to qualify as patent-eligible subject matter, an invention must accomplish a practical application.[592] With regard to the claim at issue, the method steps apply to a set of structural parameters and the result set provides a number of lead compounds with an increased probability of binding to the used protein. Hence, the method provides "a useful, concrete and tangible result" that can be used to guide further screening. Irrespective of the recitation of specific structural coordinates, the claims are directed to *in-silico* screening methods that have a practical application. Consequently, the methods must be considered statutory subject matter under the *State Street* rationale.[593]

The utility requirement of 35 U.S.C. § 101 depends on the utility of the candidate compounds identified by the screening methods. Utility is present if the specification discloses that the binding compounds may be used either to stimulate activity of protein P to reduce blood pressure or, in cases of hypertension, to inhibit the activity of protein P and thus cause an increase in blood pressure. An assertion of either or both of these uses for a protein P binding compound that is credible to one skilled in the art would be sufficient as a specific, substantial, and credible utility. Although

590 European Patent Office, Japan Patent Office, United States Patent and Trademark Office, Trilateral Project WM4, Comparative Studies in New Technologies (Biotechnology, Business Methods, etc.), Report on Comparative Study on Protein 3-Dimensional (3-D) Structure Related Claims, Vienna 2002, 37.

591 See State Street Bank & Trust Co. v. Signature Financial Group Inc., 149 F.3d 1368, 1373 (Fed. Cir. 1998). The 'useful result' aspect of the practical application test presupposes significant functionality. See Arrhythima Research Tech. v. Carazonix Gorp., 958 F.2d 1053, 1057 (Fed. Cir. 1992).

592 Managing Intellectual Property 2003, Issue 132, p. 38, In State Street the court overturned the long-accepted rule that business methods were not statutory subject matter. In favour of banks, software companies and the nascent internet industry, the court said that methods of doing business should be treated the same way as any other patentable invention. It thus extended the holding of the earlier decision, In re Alappat, 33 F.3d 1526 (Fed. Cir. 1994), which had affirmed the patentability of computer programs.

593 European Patent Office, Japan Patent Office, United States Patent and Trademark Office, Trilateral Project WM4, Comparative Studies in New Technologies (Biotechnology, Business Methods, etc.), Report on Comparative Study on Protein 3-Dimensional (3-D) Structure Related Claims, Vienna 2002, 71.

the specification describes that protein P, when active, lowers blood pressure, there is no indication of a correlation between binding activity and activation. Absent of a known or disclosed correlation between binding and activation, the identification of compounds which bind to protein P lack a specific, substantial, and credible utility.[594]

The USPTO determines the principles of enablement by considering several factors. Enablement depends on the selection, with mere general guidance, from the specification, of one or more programs to identify the binding pocket of protein P. Further, identification of the binding pocket must be demonstrated to be valid. Finally, in order for the conditions of enablement to be fulfilled there must be an expectation of success in identifying compounds that bind to protein P, and the amount and nature of experimentation required to select candidate compounds must be clear.

The office alleges that enablement is likely to fail unless the binding pocket identification is known to be highly predictive. The amount of experimentation required to identify and confirm the binding pockets is likely to be undue, since the program would yield multiple possible binding pockets. Thus, a person skilled in the art would have to choose the most likely predicted binding pockets in order to verify the actual pocket. Since the binding pocket is not confirmed prior to screening, the sets of possible binding compounds could be completely devoid of compounds that bind to protein P. Moreover, even if the claimed methods identify compounds that bind to protein P, the specification does not demonstrate the use of these compounds without undue experimentation.[595]

The USPTO further states that the claimed methods satisfy the written description requirements of 35 U.S.C. § 112, first paragraph. The specification includes the elements that are necessary to carry out the claimed method, such that one skilled in the art would have recognized that the patentee indeed possessed the claimed invention. It also teaches prior art programs that can be used to identify the binding pocket and to screen for candidate binding compounds. In addition, the specification determines the structural coordinates of protein P required by the pocket prediction and screening programs.[596]

The USPTO further claims a lack of clarity under 35 U.S.C. § 112, second paragraph, because the claim is directed to a process, but does not set forth any particular

594 European Patent Office, Japan Patent Office, United States Patent and Trademark Office, Trilateral Project WM4, Comparative Studies in New Technologies (Biotechnology, Business Methods, etc.), Report on Comparative Study on Protein 3-Dimensional (3-D) Structure Related Claims, Vienna 2002, 71.

595 European Patent Office, Japan Patent Office, United States Patent and Trademark Office, Trilateral Project WM4, Comparative Studies in New Technologies (Biotechnology, Business Methods, etc.), Report on Comparative Study on Protein 3-Dimensional (3-D) Structure Related Claims, Vienna 2002, 72.

596 European Patent Office, Japan Patent Office, United States Patent and Trademark Office, Trilateral Project WM4, Comparative Studies in New Technologies (Biotechnology, Business Methods, etc.), Report on Comparative Study on Protein 3-Dimensional (3-D) Structure Related Claims, Vienna 2002, 72.

steps involved in the process. Since the prior art did not disclose any 3-D coordinates, the U.S. office acknowledges novelty. However, prior art renders the invention obvious. The computer algorithm used to identify compounds that can potentially bind protein P is known and is unmodified. Consequently, the difference between the prior art and the claimed invention as a whole is limited to descriptive material stored on a machine. Data fed into a known algorithm whose purpose is to compare or modify those data using a series of processing steps is considered non-functional descriptive material, because there is no alteration of the process. Consequently, the claimed invention is directed to a method of using a known comparison in order to compare data sets. An invention does not become nonobvious merely because new data becomes available for analysis. Non-functional descriptive material cannot overcome nonobviousness of an invention that would have otherwise been obvious.[597]

cc) Discussion

i. The discussion on the patentability of computer-implemented inventions in Europe

For a better understanding of the EPO's decision to accept the patentability of the *in-silico* method (claim 1), it is beneficial to fully take into account the intense discussion surrounding the patentability of computer-implemented inventions taking place in Europe.[598] While the EPO has already granted large numbers of patents involving computer programs, two issues have exposed patentees and other groups to a significant risk. First, differences in national interpretations of the EPC have created a large amount of ambiguity related to the scope of protection for various classes of patents in different member states. Second, the fact that the EPC itself explicitly excludes "computer programs as such" from patentable subject matter has added to existing uncertainties. As to the latter, the EPO established its current practice to grant computer-implemented inventions by a number of decisions. In "*Computer program product/IBM*"[599] the Board of Appeals of the EPO acknowledged the patentability of computer-implemented inventions if any "further technical effect" is provided. The Board reasoned:

597 European Patent Office, Japan Patent Office, United States Patent and Trademark Office, Trilateral Project WM4, Comparative Studies in New Technologies (Biotechnology, Business Methods, etc.), Report on Comparative Study on Protein 3-Dimensional (3-D) Structure Related Claims, Vienna 2002, 73.

598 Nack, Ralph, Neue Gedanken zur Patentierbarkeit von computerimplementierten Erfindungen - Bedenken gegen Softwarepatente - ein déjà vu?, GRUR Int. 2004, 771, 771; Nack, Ralph, Sind jetzt computerimplementierte Geschäftsmethoden patentfähig? GRUR Int. 2000, 853, 853 emphasizing that the discussion increasingly focuses on the question of whether the patent system as such should be criticized.

599 T 1173/97, Computer program product/IBM, OJ 1999, 609.

> "A computer program product is not excluded from patentability under Art. 52(2) and (3) EPC if, when it is run on a computer, it produces a *further* technical effect which goes beyond the "normal" physical interaction between program (software) and computer (hardware)."[600]

The decision of *Computer program product/IBM* thus specifies the meaning of Art. 52 EPC. According to Art. 52(2) EPC, computer programs shall not be regarded as inventions within the context of Art. 52(1) EPC and are therefore excluded from patentability. Art. 52(3) EPC, however, establishes an important limitation to the scope of this exclusion: the exclusion applies only to the extent to which a European patent application or a European patent relates to programs to computers "as such".[601] Since the technical character is generally accepted as an essential requirement for its patentability within the context of the application of the EPC (see Rules 27 and 29 EPC), the exclusion of computer programs as such from patentability would mean that such programs are considered mere abstract creations, lacking in technical character.[602] Computer programs cannot be considered as having technical character for the very reason that they are software programs. This technical character, however, can be exhibited by further effects derived from the execution of the instructions given by the computer program.[603] In "*Computer program product/IBM,* the court required a particular *further* technical effect such as a piece of software managing an "industrial process", "the working of a piece of machinery" or an "internal functioning" of a computer itself.[604]

In *Two Identities/COMVIK*[605], the Board further determined that the requirement of a technical character permits the invention „to have a mix of technical and "non-technical" features, even if the non-technical features should form a dominating part."[606] An invention is patentable „even if the technical was not the dominating part of the invention. "[607]

In the following cases, the Board of Appeals of the EPO appears to weaken the standards for computer related inventions by accepting claims for computer methods "using technical means". [608] In *Microsoft*, the invention involved "a method in a computer system having a clipboard for performing data transfer of data in a clipboard format."[609] The Board determined that the invention has "technical character"

600 T 1173/97, Computer program product/IBM, OJ 1999, 609, 628-623, see also T 208/84, OJ 1987, 14; T 26/86, N. Publ.(EPO 1989); T 209/91, N. Publ. (EPO 1991); T 6/83, OJ 1990, 5; T 158/88, OJ 1991, 566; T 769/92, OJ 1995, 525; T 59/93, N. Publ (EPO 1994).

601 Schulte/Moufang, PatG mit EPÜ, § 1 No. 156.

602 Vicom/X-ray Apparatus, OJ 1987, 14; Singer/Stauder, EPC, 3rd ed., Art. 52, Nos. 36-39.

603 Benkard/Melullis, EPC, Art. 52, 207, stating that the decision finally gave up the limits originally set forth by the EPC.

604 T 1173/97, Computer program product/IBM, OJ 1999, 609, 628.

605 T 641/00, Two Identities/COMVIK, OJ 2003, 352, 356-357.

606 T 641/00, Two Identities/COMVIK, OJ 2003, 352, 356.

607 T 641/00, Two Identities/COMVIK, OJ 2003, 352, 356, see also T 935/97 Computer program product, RPC 1999, 861; T 931/95, Controlling pension benefits system, OJ 2001, 441.

608 T258/03, Auction method/Hitachi, OJ 2004, 575, 585; T 0411/03 GRUR Int. 2006, 851 – Microsoft (Board of Appeals 2006).

609 T 0411/03, GRUR Int. 2006, 851, 851 – Microsoft.

because it is "used independently of any cognitive content to enhance the internal operation of a computer" for "facilitating the exchange of data among various application programs."[610] By assisting "the user in transferring no-file data into files", the invention "solves a problem" by "technical means" and goes beyond the "elementary interaction of any hardware and software of data processing."[611]

The literature is generally consistent with the EPO's approach to accepting computer related inventions under certain circumstances.[612] *Benkard/Melullis*, however, emphasizes that the patentability standard should not be satisfied if a result or effect is merely "carried out" by a computer. Under this view, it is necessary that "a technical teaching" establishes the "technical effect" independently from the computer application.[613] *Busse/Keukenschrijver* agrees with *Benkard/Melullis*, but stresses that a technical effect cannot be caused by the mere application of software. Under this perspective it is, however, also not justified to use the fact that software is applied as an argument against a technical contribution.[614]

Once granted, however, a European patent becomes subject to the national patent laws of each country "in respect of which it is granted." (Art.64 I). According to Art. 64 III EPO, "any infringement of a European Patent shall be dealt with by national patent law. [615] The fact that a European patent to a computer-implemented invention might be challenged under the law of designated member states causes a high level of uncertainty for patent applicants and potential investors.[616] Although the basic national laws on patentability are in principle uniform as between themselves and the provisions of the European Patent Convention, the detailed interpretation is the task of the courts. In other words, they are not bound to follow the decisions of the EPO's appellate bodies and may, in the event of conflict, respect their own legal traditions.[617] With respect to the interpretation of computer-implemented inventions, this has lead to legal divergences. In contrast to the EPO case law, the U.K. jurisprudence considers computer program-related inventions which consist of a method for performing business to be not patentable, even if a technical contribution exists.[618] According to German case law, it had been assumed that the patentability of

610 T 0411/03, GRUR Int. 2006, 851, 853 – Microsoft.
611 T 0411/03, GRUR Int. 2006, 851, 853 – Microsoft.
612 Schulte/Moufang, PatG mit EPÜ, § 1 No. 156.
613 Benkard/Melullis, EPC, Art. 52 No. 219.
614 Busse/Keukenschrijver, PatG, § 1 No. 75.
615 Benkard/Jestaedt, EPÜ, § 64 No. 29-43.; as for the German practice, see Schulte/Kühnen, PatG mit EPÜ, § 139 No. 6.
616 Krieger, Albrecht, Wann endlich kommt das europäische Gemeinschaftspatent? – Zwei Brüder als Kämpfer für den Schutz des geistigen Eigentums in Deutschland, in Europa und in der Welt, GRUR 1998, 256, 259.
617 Benkard/Jestaedt, EPÜ, § 64 No. 29.
618 Merrill Lynch [1989] RPC 561 (Court of Appeal). There also exists divergence with regard to the form of possible claims allowable. The U.K patent office and German court allow program product claims in the form approved in the EPO Board of Appeal decisions Computer program product I and II, see T1173/97, OJ 1999, 609 (EPO 1998) and T0935/97, N. Publ.(EPO 1999), where an additional "technical contribution" is required. The Netherlands

business methods having a technical aspect was allowable, even if the only technical contribution that exists is non-technical.[619] This is illustrated by the cases of "*Automatic Sales Control*"[620] and "*Speech Analysis Apparatus*"[621]. Although the German Federal Supreme Court later clarified its interpretation by determining that the adequate approach is the one followed by the EPO Board of Appeals, specifically that an inventive technical contribution is decisive for the requirement of the inventive step, the earlier decisions still serve as an example of how legal interpretation may result in major changes to the scope of patentability at the national level.[622] Addressing this situation, the European Commission presented a proposal in 2002 for a Directive on the Patentability of computer-implemented inventions.[623] The major goal of this proposal was to harmonize national patent laws with respect to the patentability of computer-implemented inventions by making the conditions of patentability more transparent. Any sudden change in the legal position, in particular any extension of patentability to computer programs "as such" should be avoided.[624] The draft provoked much criticism from opponents of extensive patent protection.[625] When the directive was voted on by the European Parliament on September 24, 2003 numerous amendments were introduced which reflected concerns from diverse backgrounds. Opponents of the directive claimed that the proposal would introduce U.S.-style regimes on behalf of large companies that were able to acquire unlimited software patents. Further, the directive would open the door to trivial patents after the

patent office, by contrast, allowed a claim to computer software without any additional contribution outside the computer, stating that already the download of software on the computer creates a technically distinct machine, see Netherland Patent Office CR 1986, 541; CR 1988, 29. This conclusion, however, is contrary to Art. 52 II EPC that prohibits the patentability of computer programs "as such", see Benkard/Melullis, PatG, § 52, No. 189.

619 Nack, Ralph, Sind jetzt computerimplementierte Geschäftsmethoden patentfähig?, GRUR Int. 2000, 853.

620 Federal Patent Court, 32 IIC 328 (2001) – Automatic Sales Control (Automatische Absatzsteuerung).

621 BGH, 33 IIC 343 (2002) – Speech Analysis Apparatus (Sprachanalyseeinrichtung).

622 BGH 33 IIC 232 (2002) – Logic Verification (Logikverifikation); Benkard/Melullis, EPÜ, Art. 52 No. 209.

623 Proposal for a Directive of the European Parliament and of the Council on the patentability of computer-implemented inventions, COM(2002) 92 final of 20.2.2002; an overview is provided by Kraßer, Rudolf, Patentrecht: ein Lehr- und Handbuch zum deutschen Patent- und Gebrauchsmusterrecht, europäischen und internationalen Patentrecht, 5. Aufl., München 2004, 166-171. See also Nack, Ralph, Die patentierbare Erfindung unter den sich wandelnden Bedingungen von Wissenschaft und Technologie, München 2002, 268.

624 Proposal for a Directive of the European Parliament and of the Council on the patentability of computer-implemented inventions, COM(2002) 92 final of 20.2.2002, 11.; Nack, Ralph, Die patentierbare Erfindung unter den sich wandelnden Bedingungen von Wissenschaft und Technologie, München 2002, 271 argues that the principles set forth by the Technical Board of Appeals of the European Patent Offices should be applied, but the prohibition to patent computer programs as such abolished.

625 The Foundation for a Free Information Infrastructure (FFII) is leading a campaign against the directive, claiming it would establish a 'situation comparable to the U.S.'.

U.S. example, such as Amazon's 'one-click' method.[626] On July 5, 2005, the European Parliament, however, finally rejected the initiative. As a response to the rejection, the European Commission declared that it would not attempt to submit any more proposals related to the issue.[627]

ii. Classification of *In-Silico* Screening Methods in Europe

As stated earlier, the EPO accepts the patentability of Claim 1[628] to the *in-silico* method, arguing that an algorithm for the simulation of a 3-D protein represents a technical contribution through the use of technical data. The reasoning, however, fails to explain why an algorithm is meant to be a technical contribution. Particularly in light of the fact that neither the statutory background, nor the existing case law provides an unambiguous definition of what is understood as technical contribution, it is beneficial to consider the EPO analysis more closely. This requires a more comprehensive analysis of the invention as such that goes beyond the aspects of computer-implementation. In addition, a more precise determination of patentability requirements is necessary. The questions that arise are the following: Why does the claim at issue in an *in-silico* method establish a technical contribution sufficient for patentability? Why is it considered more than "mere technical data" or "abstract ideas", both of which would be excluded from patentability under Art.52 II (a) EPC? To find an answer to these questions, the fact that an *in-silico* claim belongs to the field of bioinformatics is of major importance. As explained earlier, bioinformatics refers to the use of computing methods to study biological processes. An *in-silico* claim visualizes a biological process, namely the creation of a protein-ligand complex and thus is covered by this category. [629]

The EPO's analysis does not address the biological aspects that are included in the claim. It merely stresses that the claim includes the use of data for computerized compound libraries. Hence, the patent office only emphasizes the computer-related aspects of the claim, but does not take into account that the data relates to a molecular biological process. The latter, however, is a central characteristic of the invention. The question of whether the invention establishes a technical contribution can-

626 Schulte/Moufang, PatG mit EPÜ, § 1, No. 161.

627 FAZ of July, 6, 2005, S. 13 (Nr. 154); TAZ of July 7, 2005, S. 8 (No. 7709).

628 A method of identifying compounds that can bind to a protein P, comprising the steps:
a) The application of a 3-dimensional molecular modelling algorithm to the atomic coordinates of protein P to determine the spatial coordinates of the binding pocket of protein P.
b) The electronic screening of the stored spatial coordinates of a set of candidate compounds against the spatial coordinates of the protein P binding pocket with the goal of identifying compounds that can bind to protein P; see European Patent Office, Japan Patent Office, United States Patent and Trademark Office, Trilateral Project WM4, Comparative Studies in New Technologies (Biotechnology, Business Methods, etc.), Report on Comparative Study on Protein 3-Dimensional (3-D) Structure Related Claims, Vienna 2002, 10.

629 Chapter 3 B III.

not be assessed without referring to the biotechnological nature of the claim. An *in-silico* screening method demonstrates the protein's ability to bind with certain compounds and thereby particularly refers to the protein's function. As explained in Chapter II, proteins perform a wide variety of functions, such as to provide catalytic activity or (in the case of receptor proteins) to detect chemical signals.[630] Since these functions define the characteristics of the biological binding process, they are critical elements of the *in-silico* method. Biological functions related to proteins typically control a wide range of processes in the living organism. The computer-based visualization of a biological function translates and transfers a biological mechanism (that is, a technical effect) into a virtual space, where the (*in vivo*) technical effect is reproduced *in silicio*. The biological function is performed independently from the computer software. The computerized protein of the claimed method *in-vivo* performs a particular biotechnological effect by binding compounds or regulating inhibitor activity. Hence, a significant effect is present outside the software-hardware relationship of the computer. Biological functions related to proteins thus must be considered "further technical effects which go beyond the normal physical interaction between software and hardware" as required under the standards developed by the EPO. [631]

Therefore, patent examiners and courts should examine bioinformatic claims, such as the one at issue directed to an *in-silico* method, in light of the simulated biological process. The patent law system should consider *in-silico* methods patentable subject matter, provided that the computerized molecule *in-vivo* performs a significant biological function. In summary, the author agrees with the EPO's decision to accept the patentability of *in-silico* methods (Claim 1). Rather than to exclusively focus on the question of whether the computerized data is used for the screening of other computerized databanks, the analysis of an *in-silico* claim should take into account the underlying biological process. If measurable biological effects exist, these should be considered adequate to establish patentability.[632]

630 Chapter 2 B.

631 T 1173/97, Computer program product/IBM, OJ 1999, 609, 618; also T 641/00, Two Identities/COMVIK, OJ 2003, 352, 356, see also T 935/97 Computer program product, RPC 1999, 861; T 931/95, Steuerung eines Pensionssystems, OJ 2001, 441; T 258/03, Auction method/Hitachi, OJ 2004, 575, 585; T 411/03 GRUR Int. 2006, 851 – Microsoft.

632 Masuoka, Kunishisa, Ways of Protecting New Technology Related Inventions in the Life Science Field, IIP Bulletin 2003, 28-34, 32. It is also suggested that the novelty of an in-silico screening process is assessed on grounds of the underlying information. Bearing technical significance, information on new tertiary protein structures should thus be considered positive element for the creation of novelty.

iii. Classification of *In-Silico* Screening Methods in the U.S.

As for the USPTO's statement, the Office confirmed the patentable subject matter due to the *State Street*[633] rationale. Under this doctrine, an invention must comply with the technological arts. To the extent that the invention is nonobvious, technological contribution is not required. The mere fact that the invention uses a computer or software is sufficient to bring it within the technical art if it also provides a "useful, concrete and tangible result".[634] Thus, a particular technical contribution provided by the invention is not required. The case of *State Street Bank & Trust Co. v. Signature Financial Group Inc.* referred to a business method which was performed with the aid of a computer. [635] Concerning this matter, the court held that three categories of subject matter are not patentable: laws of nature, natural phenomena, and abstract ideas. Consequently, mathematical algorithms as mere abstract ideas are not patentable inventions. However, once an algorithm is applied, it becomes a patentable invention if it generates tangible results.[636] In *Diamond v. Diehr*[637], the Court had determined that "certain types of mathematical subject matter, standing alone, represent nothing more than abstract ideas until reduced to some type of practical application."[638] Hence, a mathematical algorithm must be applied in a "useful way". Applying *Diamond*, the court in *State Street* held that such a useful practical application of an abstract idea is achieved provided it produces "a useful, concrete and tangible result".[639] As to the claim at issue, it must be determined whether "the mathematical algorithm is directly or indirectly recited". If a mathematical algorithm is found, it must then be decided whether it is "applied in any manner to physical elements or process steps".

The claim at issue considers a method that involves a simulated protein. The polypeptide is based on algorithm data that determine the 3-D folding structure. Being an applied algorithm and producing a useful, concrete and tangible result, the *in-silico* method falls within the *State Street* doctrine and therefore constitutes a patentable subject matter.

The USPTO rejected the claim for lack of utility, because the description does not indicate whether there is a correlation between binding activity and activation of

633 State Street Bank & Trust Co. v. Signature Financial Group Inc, 149 F. 3d 1368 (Fed. Cir. 1998).
634 State Street Bank & Trust Co. v. Signature Financial Group Inc, 149 F. 3d 1368, 1372.
635 State Street Bank & Trust Co. v. Signature Financial Group Inc, 149 F. 3d 1368, 1373; In re Lowry, 32 F.3d 1579 (Fed. Cir. 1994) (claim to data structure stored on a computerreadable medium which increases the efficiency of the computer is held to be statutory subject matter), In re Warmerdam, 33 F.3d 1354 (Fed. Cir. 1994) (claim directed to data structure per se held nonstatutory subject matter if data structure did not cause functional change in computer)
636 State Street Bank & Trust Co. v. Signature Financial Group Inc, 149 F. 3d 1368, 1375.
637 Diamond v. Diehr, 450 U.S. 175, 182 (1981).
638 In re Alappat, 33 F.3d 1526, 1557 (Fed. Cir. 1994).
639 Diamond v. Diehr, 450 U.S. 175, 182.

protein P. Thus, the Office requires the indication of a pharmaceutical effect. The need for a particular pharmaceutical effect to comply with the utility requirement had already been established in the context of the patentability of *in vitro* screening methods. Certainly, the final drug design must be considered "useful". In the context of mass screening of expansive compound libraries – as the first step in discovering the lead compound for a new drug – the only demonstrated activity of the lead compound is a mere binding affinity to the *in vitro* or computerized receptor.[640] This binding activity is essential for the determination of a "practical use", i.e., the pharmaceutical effect of a screened compound.[641] In *Cross v. Lizuka*[642] the Court of Appeals for the Federal Circuit held that the mere inhibition of an enzyme by a compound was enough to establish a "practical use".[643] In *Cross*, however, the applicant provided exact experimental data regarding the inhibition process that included information subject to the correlation of binding activity and activation, which is essential for the binding process. The specification explained the following:

> "The imidazole derivatives … of this invention are novel compounds which are not described in literature, and which possess a strong inhibitory action for thromboxane synthetase from human or bovine platelet microsomes, and which exhibit a strong inhibitory action for biosynthesis or thromboxane A sub2 in mammalia including human. In general, a satisfactory inhibitory effect is found at a level of molar concentrations of 2.5 x 10-8, for example, 2-[p-(1-imidaoylmethyl) phenoxy]-acetic acid hydrochloride produce the about 50% inhibitory effect at the molar concentration of 2.5 x 10-8. Accordingly, the imidazole derivatives of this invention are extremely useful as therapeutical medicines for diseases caused by thromboxane A sub2, such as inflammation, hypertension, thrombus, cerebral apoplexy, asthma, etc."[644]

Based on this information, the court found that the screened compounds provided sufficient data to comply with the utility requirement.[645] The claim at issue, by contrast, lacks any experimental data and thus cannot provide any "practical use". The *in-silico* method itself, which is described by the claim language, only provides hypothetical information. The applicant had to provide additional *in vitro* testing in order to verify that the underlying technical problem of finding useful agents indeed had been solved.[646] The given specification does not disclose any working examples. It should provide more information pertaining to the actual screened compound and not only to the method itself.

As to enablement, the USPTO stated that the given claim does not satisfy the "how to make" prong of 35 U.S.C. § 112. The factors the USPTO considers with regard to enablement follow the principles the Federal Circuit developed in *In re*

640 Ducor, Phillippe, New drug discovery technologies and patents, 22 Rutgers Computer and Technology law journal (RUCTLJ) 1996, 369, 425.
641 Ducor, Phillippe, New drug discovery technologies and patents, 22 Rutgers Computer and Technology law journal (RUCTLJ) 1996, 369, 425.
642 Cross v. Lizuka 753 F.2d 1040 (Fed. Cir. 1985).
643 Cross v. Lizuka 753 F.2d 1040, 1046.
644 Cross v. Lizuka 753 F.2d 1040, 1044.
645 Cross v. Lizuka 753 F.2d 1040, 1049.
646 Lonati, Milena, Patentability of receptors and screening methods: does in silico screening pose new legal problems?, Bioscience Law Report 2000/2001, 144, 145.

Wands.[647] The enablement standard developed in *In re Wands* includes the quantity of experimentation necessary to practice the claimed invention, the amount of guidance presented in the specification, the presence or absence of working examples, and the predictability or unpredictability of the art.[648]

In addition, the Federal Circuit in *University of Rochester v. G.D. Searle & Co* established the principle that even if a three-dimensional structure of a protein is known it is not possible for an ordinary skilled person to predict a candidate compound for the binding pocket without undue experimentation.[649] The court stated that this could be different in a case based on the complementariness of a nucleic acid and a protein. In non-genetic situations, that correspondence could be less clear. In this context, the Federal Circuit reasoned:

> "Given the sequence of a single strand of DNA or RNA, it may therefore have become a routine matter to envision the precise sequence of a "complementary" strand that will bind to it. (…). Even with the three-dimensional structures of enzymes such as COX-1 and COX-2 in hand, it may even now not be within the ordinary skill in the art to predict what compounds might bind to and inhibit them."[650]

Since the specification does not teach the use of potential candidate compounds which respond to the computerized screening method, the "how to use" prong of Section 112 is not satisfied, either. A strong correlation exists between the "how to use" prong of the enablement requirement and the requirement for a disclosure of practical utility found in 35 U.S.C. § 101. This principle has been confirmed in various decisions.[651]

The claim does not meet the threshold requirement of clarity and precision under 35 U.S.C. Section 112, second paragraph. Since the potential candidate compounds are not being included in the claim language, the application does not describe the particular subject matter of the invention. The scope of the invention sought to be patented is the finding of lead compounds as one step of the screening process. The claim only refers to the application of the algorithms in order to simulate the three-dimensional structure and to the potential screening of binding compounds. The ac-

647 In re Wands, 858 F.2d 731 (Fed. Cir. 1988).

648 In re Wands, 858 F.2d 731, 731.

649 University of Rochester v. G.D. Searle & Co.; Inc, 358 F.3d 916, 925 (Fed. Cir. 2004).

650 University of Rochester v. G.D. Searle & Co.; Inc, 358 F.3d 916, 925. Actually the court set its argument in the context of the written description factor. However, since there is a "significant overlap" between both requirements, the statement can also be applied with regard to enablement, University of Rochester v. G.D. Searle & Co.; Inc, 358 F.3d 916, 921 (citation omitted).

651 Process Control Corp. v. Hyd Reclaim Corp., 190 F.3d 1350, 1358 (Fed. Cir. 1999) ("If a patent claim fails to meet the utility requirement because it is not useful or operative, then it also fails to meet the how-to-use aspect of the enablement requirement."); In re Brana, 51 F3d 1560, 1569 (Fed. Cir. 1995) (classifying practical utility as an implicit requirement of the enablement provision); Brooktree Corp. v. Advanced Micro Devices, Inc., 977 F.2d 1555, 1571 (Fed. Cir. 1992) (clarifying that if the subject matter of a patent is inoperable, then the patent may fail to meet both the utility requirement and the enablement requirement).

tual binding process is not part of the claim language. In *In re Wiggins* the Federal Court concluded that

> "If the scope of the invention sought to be patented is unclear from the language of the claim, a rejection will lie under the second paragraph of 35 U.S.C. 112"[652]

The USPTO further rejects the claim for rendering the invention obvious under Section 103. The office applied the "Examination Guidelines for Computer-Related-Inventions" of February 28, 1996[653], which describe computerized data as falling between "functional descriptive material" and "non-functional descriptive material". The Guidelines define "functional descriptive material" as "data structures and computer programs, which impart functionality when encoded on a computer-readable medium." "Non-functional descriptive material, in contrast, "includes but is not limited to music, literary works and a compilation or mere arrangement of data". As to obviousness, the Guidelines state:

> "[A] rejection of the claim as a whole under § 103 is inappropriate unless the functional descriptive material would have been suggested by the prior art. Non-functional descriptive material cannot render non-obvious an invention that would have otherwise been obvious."[654]

The guidelines further provide:

> "[A] process that differs from the prior art only with respect to non-functional descriptive material that cannot alter how the process steps are to be performed is not sufficient to achieve the utility of the invention."[655]

The principles applied by the USPTO correspond with existing case law of the CAFC. In *In re Gulack,* the court stated that when descriptive material is not functionally related to the substrate, the descriptive material will not distinguish the invention from the prior art in terms of patentability.[656] In *Ex parte Carver,* by contrast, the court characterized the given material as "functionally-descriptive, because the signals at issue were used to actuate and control sound recording responsive device structure to produce the appellant's disclosed acoustic phenomena.[657]

From a comparative point of view, the USPTO maintains a stricter approach than the EPO. Although both the U.S. and the European patent offices classify the claim as computer-implemented invention, the USPTO concludes that the claim must be rejected for rendering the invention obvious. The Office argues that the 3-D protein data is fed to an algorithm that is already state of the art. Absent any alteration or modification of the algorithm, the office concludes that the invention is obvious.

652 In re Wiggins, 488 F.2d 538, 541 (C.C.P.A. 1973).
653 Examination Guidelines for Computer-Related-Inventions, [Federal Register: February 28, 1996 (Volume 61, Number 40) 7478-7492, available at: http://www.kuesterlaw.com/swguide.htm, last checked on January 21, 2008.
654 Examination Guidelines for Computer-Related-Inventions, VI, available at: http://www.kuesterlaw.com/swguide.htm, last checked on January 21, 2008.
655 Examination Guidelines for Computer-Related-Inventions, VI, available at: http://www.kuesterlaw.com/swguide.htm, last checked on January 21, 2008.
656 In re Gulack, 703 F.2d 1381, 1385 (Fed. Cir. 1983).
657 Ex parte Carver, 227 USPQ 465, 470 (Bd. Pat. App. & Int. 1985).

Given that there is no functional relationship between the data and the algorithm, the office considers the 3-D protein structure non-functional descriptive data.

Is such a classification, however, adequate for an obviousness standard in the field of bioinformatics? [658] Pursuant to 35 U.S.C. § 103, a patent claim is rejected "if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains".[659] The statute clearly states that the invention must be considered "as a whole." The inventions at issue, however, do not only refer to the data itself. Rather, they include the simulation of a complex biological process, namely the emulation of a protein and of its binding ligands. They not only establish the descriptive data as such, but also the imitation of a biological operation performed by such data. One could argue that the USPTO fails to sufficiently take into account these biological features expressed by the data, and, consequently, does not consider the patented subject matter "as a whole."

For an evaluation of the entire invention, the key question must be whether a person skilled in the art is able to (a) predict the protein-ligand complex and (b) simulate it through the claimed *in-silico* method without involving inventive activity. In the claim at issue, the prior art does not include any similar *in-silico* screening method. In addition, the data necessary to simulate the protein by applying the algorithm must be obtained through extensive *in-vitro* testing. Consequently, neither part (a) nor part (b) of the above question can receive a positive answer, implying that the claim would not render the invention obvious. Against this background, it appears reasonable to argue that the claim should be accepted under the U.S. patent law system.

b) Claim 2

Claim 2 of the set of claims being directed to "*in-silico* screening methods" reads as follows:

> A method of identifying compounds which can bind to protein P by comparing the 3-D structure of candidate compounds with a specific 3-D molecular model which comprises the following steps:
>
> The given 3-D molecular model shows the positions of heteroatoms in the amino acids building out of the binding pockets of protein P (i.e., amino acids 223, 224, 227, 295, 343, 366, 370, 378, 384) wherein said hydrogen bonds can form hydrogen bonds with hydrogen bonding functional groups in a candidate compound.

658 Vorndran, Charles/Florence, Robert L., Bioinformatics: Patenting the Bridge between Information Technology and the Life Sciences, 93 IDEA - The Journal of Law and Technology 2003, 93, 121.

659 Chapter 3 A II 4 a.

Steps (1) through (n) describe a data processing method in which

(a) the coordinate data of the 3-D molecular model is input in a data structure such that the interatomic distances between the atoms of protein P are easily retrieved.

(b) the distances between hydrogen-bonding heteroatoms of different candidate compounds and the heteroatoms that form the binding pocket in the 3-D molecular model are compared thereby allowing the identification of those candidate compounds which would theoretically form the most stable complexes with the 3-D molecular model binding pockets of protein P, based on optimal hydrogen bonding between the two structures.[660]

aa) Background

Protein P is an established protein whose amino acid sequence is also clear. The description explains that the activity of protein P was previously known to result in lowering blood pressure. The description gives the atomic coordinates of protein P as a co-crystal with its natural ligand, and gives a logical explanation that the active residues in the binding pocket of protein P consists of specific and determined amino acids. The description demonstrates how the 3-D molecular model incorporates the 3-D structure of the binding pocket. It provides working examples of the claimed methods in which a number of compounds are identified. It also provides experimental data of the actual binding affinities of the compounds identified. Pursuant to that data, a skilled person would infer that the claimed method may be used to identify a number of compounds which bind sufficiently to protein P such that a biological effect results. No prior art suggested the 3-D coordinates of protein P. However, the prior art included *in-silico* screening programs that compare the 3-D structure of candidate compounds with the 3-D molecular model of the binding pocket of a protein of interest. Prior art also demonstrates the method of storing coordinates data to optimize the interatomic distance information.[661]

bb) Patent Offices' Analysis

The EPO states that the invention disclosed is patentable. The claim refers to a method having a link to a technical contribution that is characterized by technical features. This activity is not regarded as a presentation of information or as a pure mathematical method, excluded by Art. 52(2)(d) or (a) of the EPC, respectively, but rather as the use of the structural data. Because the description reports experimental

660 European Patent Office, Japan Patent Office, United States Patent and Trademark Office, Trilateral Project WM4, Comparative Studies in New Technologies (Biotechnology, Business Methods, etc.), Report on Comparative Study on Protein 3-Dimensional (3-D) Structure Related Claims, Vienna 2002, 10ff.

661 European Patent Office, Japan Patent Office, United States Patent and Trademark Office, Trilateral Project WM4, Comparative Studies in New Technologies (Biotechnology, Business Methods, etc.), Report on Comparative Study on Protein 3-Dimensional (3-D) Structure Related Claims, Vienna 2002, 11ff.

data that includes information about identified compounds, the requirements of clarity, enablement and support are satisfied. Novelty, inventive step, and industrial application are present, since the prior art did not disclose or suggest the 3-D coordinates of protein P. The claimed method is considered to be novel, nonobvious and industrially applicable.[662]

The USPTO also agrees that a patentable subject matter is given. In addition, the utility requirement of the claimed methods is satisfied, since the utility of the candidate compounds identified through screening is also provided. With regard to the enablement factor, the USPTO differs from the EPO. The Office held that the specification adequately described and enabled one skilled in the art to make the claimed method of screening, by virtue of working examples that identified compounds that bind to protein P. The working examples provide sufficient guidance regarding the screening program. In addition, they show the effectiveness of the screening program in using the disclosed 3-D coordinates of protein P to identify ligands binding with sufficient affinity such that a biological effect would be expected by one skilled in the art. With respect to the "how-to-use-prong" of the enablement requirement, the specification demonstrates that protein P, when active, lowers blood pressure. However, there is no indication as to whether there is a correlation between binding activity and the modulation of blood pressure. The USPTO, nevertheless, states that if compounds binding protein P could be used to modulate blood pressure without undue experimentation, the claimed method would comply with the enablement requirement of 35 U.S.C. § 112.[663]

The Office further concluded that the claim can be considered novel. The claims are obvious with regard to the prior art if the claimed data-processing method used to identify compounds that can potentially bind protein P, i.e., steps (1) through (n), would have been obvious to one skilled in the art. Consequently, the claimed method would have been *prima facie* obvious over the prior art because steps (1) through (n) appear in the prior art methods.[664]

662 European Patent Office, Japan Patent Office, United States Patent and Trademark Office, Trilateral Project WM4, Comparative Studies in New Technologies (Biotechnology, Business Methods, etc.), Report on Comparative Study on Protein 3-Dimensional (3-D) Structure Related Claims, Vienna 2002, 37.

663 European Patent Office, Japan Patent Office, United States Patent and Trademark Office, Trilateral Project WM4, Comparative Studies in New Technologies (Biotechnology, Business Methods, etc.), Report on Comparative Study on Protein 3-Dimensional (3-D) Structure Related Claims, Vienna 2002, 73.

664 European Patent Office, Japan Patent Office, United States Patent and Trademark Office, Trilateral Project WM4, Comparative Studies in New Technologies (Biotechnology, Business Methods, etc.), Report on Comparative Study on Protein 3-Dimensional (3-D) Structure Related Claims, Vienna 2002, 74f.

cc) Discussion

The *in-silico* methods of Claim 2 differ from the prior *in-silico* related invention (Claim 1) in two ways. First, the language of Claim 2 includes information related to identified compounds which are defined by size and shape. Second, the description provides particular working examples that report the specific binding process. Thus, the differences are all related to compounds that respond to the screening process. Both offices treat the claim slightly differently than Claim 1. The EPO accepts the claim due to the working examples that are reported in the description. Sufficient disclosure (Art. 83 EPC) and support (Art. 84) requirements are thus met. The USPTO concurs with the EPO regarding the written description and enablement requirement, but maintains its divergent view regarding the definition of algorithms data as non-functional data. Therefore, the USPTO rejects the claim due to obviousness.

Yet, the results being developed by both offices must be reconsidered. The question of whether the applicant is allowed to claim protection for the compounds that can be identified by a screening process has been the subject of various discussions, in particular in the context of "reach-through" claiming. Reach-through claiming refers to claim language which is broad enough to dominate future compound discoveries that can be used for rational drug design.[665] With regards to the claim at issue, it remains to be established whether it fulfills the currently required measurements of case law. A series of decisions in biotechnology cases developed a very demanding written description requirement and a high standard for enablement. The claim at issue cannot be considered a typical reach-through claim. The applicant does not simply claim all molecules performing the function of binding the receptor, without providing any information regarding the structure of the ligand. By contrast, the claim provides theoretical information about the size and shape of binding sites of the computerized method and of responding compounds, which are based on protein analysis techniques such as protein crystallization. Thus, the claim reports a description of the structure necessary to complete the entire screening. The strategy followed by the patent claimer certainly succeeds in overcoming reach-through claiming problems. Nevertheless, recent decisions of the Federal Circuit as well as of the Technical Board of Appeal have taken a very severe approach toward claim scope. In addition, it was previously demonstrated that one panel at the Federal Circuit Court ruled in favor of a demanding written description requirement. The currently required high standards for enablement establish high demands for developers of *in-silico* methods, regardless of whether the illustrated dispute can be decided on behalf of such a separate obligation. Thus, the drafting method of the claim at issue is fraught with a number of scientific and legal hazards. Even though the applicant provides working examples which prove that his speculations regarding the structure of functional ligands are correct, the prior art may bear surprises rendering the patent

665 OECD, Genetic Inventions, Intellectual Property Rights and Licensing Practices, Paris 2002, 63.

invalid. A broad claim to a set of compounds lacks novelty even if a single member of the genus was reported in the prior art. This principle applies even if the properties of the prior art compound causing it to fall within the scope of the claim were merely inherent, and not reported. Provided only one prior art ligand bears the shape and size demonstrated by the claim, and therefore responds to the *in-silico* protein, the patent is invalid. Many molecules have been reported by prior art, but relatively few have been defined by size and shape. Straight-forward searches are rarely able to identify compounds falling within the scope of claims that are defined in terms of fit within a reported binding pocket.[666]

Finally, it must be stressed that patentability on *in-silico* screening methods can only succeed in relation to the patentability of the target used in the method. The entire screening method is not completed until the compound is identified. The discovery of a new receptor, however, is the key ingredient of the screening method; the other steps are merely routine.[667]

2. Structural Data of proteins per se

a) Claims and Claim Background

Another method of drafting claims in proteomics is to refer to the 3-D structural data of the protein *per se.* The claims of the trilateral study WM4 concerning 3-D structural data of the protein *per se* read as follows.

> Claim 1:
>
> A computer model of protein P generated with the atomic coordinates listed in a specific figure.
>
> Claim 2:
>
> A data array comprising the atomic coordinates of protein P as set forth in Fig. 1 which, when acted upon by a protein modeling algorithm, yields a representation of the 3-D structure of protein P.
>
> Claim 3:
>
> A computer-readable storage medium encoded with the atomic coordinates of protein P as shown in Fig. 1.

The specification classifies protein P as novel. Experimental data is provided and it is explained that the protein, when active, lowers blood pressure. The pro-

666 Eisenberg, Rebecca S., Reaching through the Genome, In: Perspectives on Properties of the Human Genome Project; Kieff, F. Scott Ed. Amsterdam, 2003; 209, 225.

667 Lonati, Milena, Patentability of receptors and screening methods: does in silico screening pose new legal problems?, Bioscience Law Report 2000/2001, 144, 144.

tein modeling algorithms are well known in the prior art. The description provides the atomic coordinates of protein P, and asserts that the coordinates can be used for *in-silico* screening methods. The prior art does not include any reference that teaches or suggests protein P.[668]

b) Patent Offices' Analysis

As for claim 1, the EPO reasons that a computer model is not considered to be a patentable invention, since it merely presents the atomic coordinates of a single protein molecule as such. The model does not offer any technical problem solution and does not provide any further technical effect. Consequently, the claim at issue does not meet the requirements of a patent-eligible subject matter under Art. 52(2)(d) EPC, which excludes presentations of information from patentability. Further, the EPO states that the claimed invention does not provide sufficient information for an adequate prior art search. Consequently, a search cannot be carried out under Art. 54 EPC. Hence, it is not necessary to examine whether such a prior art search would identify any references that demonstrate or suggest protein P.[669]

With regard to Claim 2, the EPO states that the claimed invention cannot be considered as a patentable subject matter, since a data array is a mere presentation of information and excluded under Art. 52(2)(d) EPC.[670]

As for Claim 3, the EPO states that a storage medium does not qualify for a patent-eligible subject matter pursuant to Art. 52(2)(d), because it only determines the atomic coordinates of a single protein molecule in space, without providing a particular technical character. The data merely includes cognitive content in a generalized manner.[671] The EPO notes that the claim is distinct from cases in which the Technical Board of Appeals had acknowledged computer storage to be patentable. In con-

668 European Patent Office, Japan Patent Office, United States Patent and Trademark Office, Trilateral Project WM4, Comparative Studies in New Technologies (Biotechnology, Business Methods, etc.), Report on Comparative Study on Protein 3-Dimensional (3-D) Structure Related Claims, Vienna 2002, 7.

669 European Patent Office, Japan Patent Office, United States Patent and Trademark Office, Trilateral Project WM4, Comparative Studies in New Technologies (Biotechnology, Business Methods, etc.), Report on Comparative Study on Protein 3-Dimensional (3-D) Structure Related Claims, Vienna 2002, 34.

670 European Patent Office, Japan Patent Office, United States Patent and Trademark Office, Trilateral Project WM4, Comparative Studies in New Technologies (Biotechnology, Business Methods, etc.), Report on Comparative Study on Protein 3-Dimensional (3-D) Structure Related Claims, Vienna 2002, 34.

671 European Patent Office, Japan Patent Office, United States Patent and Trademark Office, Trilateral Project WM4, Comparative Studies in New Technologies (Biotechnology, Business Methods, etc.), Report on Comparative Study on Protein 3-Dimensional (3-D) Structure Related Claims, Vienna 2002, 35.

trast to the claim at issue, the particular data referred to a computer program with a further technical effect.[672]

The USPTO holds that Claim 1 is not tangibly embodied and thus must be considered as non-functional descriptive material *per se*. Since descriptive material is considered as an abstract idea, the claim at issue cannot be acknowledged as patentable subject matter pursuant 35 U.S.C. § 101.

As to Claim 2, the USPTO states that it is directed to a mere compilation or arrangement of data. With the 3-D coordinates consisting of non-functional descriptive material without physical structure, they must be interpreted as abstract ideas which do not qualify as patentable subject matter. See *In re Warmerdam*[673], where the court stated that descriptive material *per se* is not patent-eligible subject matter. As to the specification, the decisive element is that the atomic coordinates of protein P can be used for *in-silico* screening methods. Presupposing that the identified compounds can provide a specific, substantial, and credible utility, the claim at issue meets the utility requirement. However, such a specific, substantial, and credible utility cannot be acknowledged when the correlation between binding activation and compounds binding protein P are not disclosed. The specification only determines that protein P, when active, lowers blood pressure. It fails to provide any detailed information regarding binding activity or inhibitor regulation. A sufficient disclosure must include information about how the compounds can be used. Their use could either be directed to a stimulation of proteins P's activity to reduce blood pressure, or, in cases of hypotension, to an inhibition of the activity of protein P causing an increased blood pressure. Absent of any of these assertions, a specific, substantial, and credible utility is not acceptable.[674] The enablement requirement is satisfied. Based on the disclosure that protein modeling algorithms are well known in the art, and the complete description of the atomic coordinates of protein P, claims 1 and 2 are enabled for how to make the claimed method and are adequately described.

The how-to-use prong is not satisfied by the disclosure, unless the patent specification provides information regarding the binding activity or inhibitory regulation amounting to a specific, substantial, and credible utility. Regarding enablement, the patent description must teach one skilled in the art to use the claimed invention without undue experimentation.[675]

672 T 1173/97, OJ 1999, 609, the EPO applied its guidelines, see Guidelines for Examination in the EPO, Part C-IV.2

673 In re Warmerdam; 33 F.3d 1354, 1361, 31 USPQ2d 1754, 1760 (Fed. Cir. 1994).

674 European Patent Office, Japan Patent Office, United States Patent and Trademark Office, Trilateral Project WM4, Comparative Studies in New Technologies (Biotechnology, Business Methods, etc.), Report on Comparative Study on Protein 3-Dimensional (3-D) Structure Related Claims, Vienna 2002, 63.

675 European Patent Office, Japan Patent Office, United States Patent and Trademark Office, Trilateral Project WM4, Comparative Studies in New Technologies (Biotechnology, Business Methods, etc.), Report on Comparative Study on Protein 3-Dimensional (3-D) Structure Related Claims, Vienna 2002, 63.

With regard to Claim 3, the USPTO maintains that the structural data of protein must be considered non-functional descriptive material because the claimed invention only refers to protein data stored on a computer-readable medium. It is merely stored so as to be read by a computer without creating any functional interrelationship, either as part of the stored data or as part of the computing processes carried out by the computer. Thus, the 3-D coordinates do not impart functionality to either the data or the computer. With non-functional descriptive material being stored in a computer-readable medium as an abstract idea, it cannot be defined/classified as patent eligible subject matter pursuant to 35 U.S.C. § 101.[676] As mentioned above, the specification does not include any functionality related to either the data or the computer, and therefore must be understood as non-functional descriptive material. Descriptive material that is not functionally related to the substrate does not distinguish the invention from the prior art for patentability purposes.[677]

c) Discussion

In contrast to the treatment of *in-silico* methods, the EPO rejects the claims for lack of a further technical effect. The USPTO again classifies the claims as merely including non-functional descriptive material and rejects the claims due to obviousness. Applying the reasoning established in *In re Warmerdam*, the USPTO concludes that no patentable subject matter is established. The question in *In re Warmerdam* is whether the claim directed to a specific data process goes beyond the simple manipulation of abstract ideas. Absent any such effect, no patentable subject matter could be acknowledged.[678]

The approach taken by both patent offices is consequent in light of their general practices regarding the treatment of databases.[679] Nevertheless, scientists could ar-

676 European Patent Office, Japan Patent Office, United States Patent and Trademark Office, Trilateral Project WM4, Comparative Studies in New Technologies (Biotechnology, Business Methods, etc.), Report on Comparative Study on Protein 3-Dimensional (3-D) Structure Related Claims, Vienna 2002, 64.

677 European Patent Office, Japan Patent Office, United States Patent and Trademark Office, Trilateral Project WM4, Comparative Studies in New Technologies (Biotechnology, Business Methods, etc.), Report on Comparative Study on Protein 3-Dimensional (3-D) Structure Related Claims, Vienna 2002, 64.

678 In re Warmerdam , 33 F.3d 1354, 1361.

679 In Europe, investment in the compilation of the data might be protected under sui generis rights. The use of a considerable amount of data will only be allowed with the permission of the database owner. In practice, access to these databases will be subject to payment of a licensing fee. Due to a lack of originality, the data as such, i.e., the mere sequence as pieces of written information, are not protectable under copyright. Consequently, the information of the sequences may be used freely, see Bostyn, Sven J.R., Living in an (im)material world: bioinformatics and intellectual property protection, 01 Journal of International Biotechnology Law 2004, 2-10; 54-61, 59. For a precise and detailed overview of German and international approaches to database protection see further Nack, Ralph, Nationaler und internatio-

gue that the patent offices do not sufficiently take into account biophysical concepts, such as the importance of non-covalent bonds,[680] native vs. denatured states of proteins, etc. Patent offices allow patents on standard chemical formulae which are, in fact, merely 2-D coordinates of molecules combined together with some standard rules of chemical connectivity. 3-D coordinates of proteins, by contrast, are not deemed to be patentable, although they too demonstrate standard rules of chemical connectivity between the atoms. From a legal perspective, the offices distinguish between computer storable data and the established chemical practice to determine compounds by a chemical formula. From a scientists' perspective, however, it appears that the dimensionality (i.e., 1-D, 2-D, 3-D) in which the coordinates are represented determines the patentability of a molecule.[681]

3. Compounds identified by *in-silico* screening methods

Advances in proteomics resulted in the discovery of great numbers of new protein "targets". Due to new computerized methods, compound libraries could be increased in size. Progress in the development of screening assays, particularly "high-throughput screening" technologies (HTS)[682], enables scientists to screen such libraries for their potential protein targets and effects within a very short time.[683] The design and development of screening methods, which must be considered as research tools, is generally time-consuming and expensive.

Furthermore, economic value emerges only after years of investment and only in the case that the development of a new drug succeeds. The use of the screening target is usually made at a stage in which further steps of drug design are not yet foreseeable.[684] If the sale of the pharmaceutical is successful, however, high revenues

naler Rechtsschutz von Datenbanken (Q182), GRUR 2004, 227. The treatment of data through mechanism other than patent law is no major subject of this study.

680 Covalent bonds arise as a result of the sharing of one or more pairs of bonding electrons.

681 Vinarov, Sara D., Patent protection for structural genomics-related inventions, Journal of structural and functional genomics 2003, 191, 203.

682 A "high throughput screening" is a computerized technique of rapidly searching for molecules with desired biological effects from very large compound libraries (up to 60,000 per day), see Burke, Adrienne J., Blowing a Path for HTP Proteomics, Genome Technology 2003, 24, 24; Bader, Joel S./Chaudhuri, Amitabha/Rothberg, Jonathan M./Chant, John, Gaining confidence in high-throughput protein interaction networks, 22 Nature Biotechnology 2004, 78.

683 Wolfram, Markus, 'Reach-Through Claims' and 'Reach-Through licensing' - Wie weit kann Patentschutz auf biotechnologische Research Tools reichen? Mitteilungen der deutschen Patentanwälte 2003, 57, 58.

684 See Figure 8 at Chapter 2 E III 3.

can be expected. It is thus understandable that the owners of research tools are interested in receiving a share of such profits.[685]

Inventors attempt to protect the products they develop with the help of their research tools, such as *in-silico* methods, by including the identified compounds in the claim language.

a) Claims

A claim involving the described method may be drafted as follows:

> Compounds[686] identified by
>
> A method of identifying compounds that can bind to a protein P, comprising the steps of:
>
> a) The application of a 3-dimensional molecular modeling algorithm to the atomic coordinates of protein P to determine the spatial coordinates of the binding pocket of protein P.
>
> b) The electronic screening of the stored spatial coordinates of a set of candidate compounds against the spatial coordinates of the protein P binding pocket with the goal of identifying compounds that can bind to protein P.[687]

b) Patent Offices' Analysis

The EPO holds that the claim meets the requirement of a patentable subject matter since it refers to identified compounds. When the claimed invention does not provide enablement over the entire range of claimed embodiments, the requirement of sufficient disclosure is not met. A prior art search is limited to the example provided by the description.[688] The invention cannot be considered novel, since the natural ligand is already state of the art and thus prejudicial to novelty.

685 Wolfram, Markus, 'Reach-Through Claims' and 'Reach-Through licensing' - Wie weit kann Patentschutz auf biotechnologische Research Tools reichen?, Mitteilungen der deutschen Patentanwälte 2003, 57, 58.

686 Claim 2 of the same case.

687 European Patent Office, Japan Patent Office, United States Patent and Trademark Office, Trilateral Project WM4, Comparative Studies in New Technologies (Biotechnology, Business Methods, etc.), Report on Comparative Study on Protein 3-Dimensional (3-D) Structure Related Claims, Vienna 2002, 10. Another U.S. patent No. 6,083,711 entitled "Proteases compositions capable of binding to said site, and methods of use thereof" covers compounds screened by 3-D in-silico structure defined by structural coordinates, see Eisenberg, Rebecca S., Reaching through the Genome, In: Perspectives on Properties of the Human Genome Project; Kieff, F. Scott Ed. Amsterdam, 2003; 209, 225.

688 European Patent Office, Japan Patent Office, United States Patent and Trademark Office, Trilateral Project WM4, Comparative Studies in New Technologies (Biotechnology, Business Methods, etc.), Report on Comparative Study on Protein 3-Dimensional (3-D) Structure Related Claims, Vienna 2002, 37.

The USPTO concludes that Claim 2 refers to a statutory subject matter. The claim only satisfies the utility requirement of 35 U.S.C. § 101 if the specification teaches that the binding compounds may be used to either stimulate activity of protein P to reduce blood pressure, or in cases of hypotension, inhibit the activity of protein P to cause an increase in blood pressure. Nevertheless, the claim must be rejected, both due to a lack of enablement and of a sufficient description under the principles developed in *Regents of the University of California v. Eli Lilly*.[689] Since one skilled in the art would come to the conclusion that the inventors were not in possession of the claimed invention, the claim fails to comply with the written description requirement. It is not sufficient that the claim at issue is directed to a "compound identified by an in-silico method"; rather the claim language has to include specific structural or functional characteristics.[690]

The USPTO further determines that the claim does not comply with the enablement requirement for the "how-to-make" prong of 35 U.S.C. § 112, first paragraph. The patent lacks a disclosure of any particular structure for the claimed compound. The specification does not provide any guidance or working example in this unpredictable art. Thus, an artisan would not have been unable to make the claimed compound without undue experimentation. An assay for finding a product is not equivalent to a positive recitation of how to synthesize such a product. The USPTO maintains that the claimed invention does not comply with the "how to use" prong of 35 U.S.C. § 112, first paragraph. The specification does not show how to administer the claimed compound so as to effect a viable blood pressure treatment regimen. Treatment/administration protocols depend upon the nature of the compound being administered as well as the clinical condition of the patient. In the absence of additional information, a skilled person would not have been able to use the undisclosed compound(s) for treatment without undue experimentation.

As for novelty, Claim 2 is rejected as anticipated by the prior art compound, particularly if a search yielded one of the compounds tested experimentally in the specification. It would be rejected as being anticipated, or rendered *prima facie* obvious by the prior art under two conditions. First, the prior art demonstrates agonists or antagonists of protein P, and second, the examiner can provide evidence to support the judgment that prior art compounds inherently fall within the scope of the claim.[691]

With regard to the written description requirement, the USPTO holds that the claim at issue is directed to a genus of compounds identified by the method of Claim 2. Moreover, the specification discloses at least some examples of the structure of compounds within the scope of the claim. Nevertheless, there is no evidence of a

689 Regents of the University of California v. Eli Lilly, 119 F.3d 1559 (Fed. Cir. 1997).

690 Regents of the University of California v. Eli Lilly, 119 F.3d 1559.

691 European Patent Office, Japan Patent Office, United States Patent and Trademark Office, Trilateral Project WM4, Comparative Studies in New Technologies (Biotechnology, Business Methods, etc.), Report on Comparative Study on Protein 3-Dimensional (3-D) Structure Related Claims, Vienna 2002, 76.

structure/function relationship *per se* between the disclosed compounds and any others that might be found using the claimed method. Structurally identified characteristics of the genus members are not disclosed. Thus, the claimed invention is not supported by a sufficient written description. The rejection might be overcome with a demonstration of objective evidence. This evidence must support the proposition that the selected disclosed compounds are representative of the structure of the group of molecules identified by the claimed method.[692]

c) Discussion

aa) Reach-through-Claims

Both offices classify the claim as a reach-through claim.[693] Consequently, they treat it similarly to inventions involving identified compounds of *in-vitro* screening methods.[694] The question is whether such claims are patentable. Reach-through claims use a claim language broad enough to include future product discoveries without providing any information, such as structure coordinates or other elements.[695] The inventor does not only claim the structure of a protein, but also of compounds that bind to the protein, even though the latter is still unknown at the time the claims are drafted. In terms of *in-silico* methods, the applicant not only claims the computerized screening method, but also the compounds, which might be identified by such methods.[696] The topic of reach-through claims has been the subject of various discussions.[697] After an increasing number of applications contained claims drawn to

692 European Patent Office, Japan Patent Office, United States Patent and Trademark Office, Trilateral Project WM4, Comparative Studies in New Technologies (Biotechnology, Business Methods, etc.), Report on Comparative Study on Protein 3-Dimensional (3-D) Structure Related Claims, Vienna 2002; Vinarov, Sara D., Patent protection for structural genomics-related inventions, Journal of structural and functional genomics 2003, 191, 205.

693 As for reach-through claims, see Straus, Joseph, Reach-through claims and research tools as recent issues of patent law in: Estudios sobre propiedad industrial e intellectual y derecho de la competencia, Curell Suñol, M./et al. (Eds.): Grupo Español de la AIPPI, Barcelona, 2005, 921. The need of inventors to protect screened proteins emerged in the 'post-genomic' era where proteins capable of becoming the targets of drug development are identified rapidly and in large quantities. This is also emphasized in Masuoka, Kunihisa, Study on the Ways of Protection of Post-Genome Research Products, IIP Bulletin 2002, 84, 89.

694 As "in-vitro" is understood "outside the living body and in an artificial environment"; see at Medline Plus, Medical Dictionary, available at: http://www2.merriam-webster.com/cgi-bin/mwmednlm?book=Medical&va=in%20vitro, last checked on January 21, 2008.

695 OECD, Genetic Inventions, Intellectual Property Rights and Licensing Practices, Paris 2002, 63.

696 Lonati, Milena, Patentability of receptors and screening methods: does in silico screening pose new legal problems?, Bioscience Law Report 2000/2001, 144, 145.

697 Eisenberg, Rebecca S., Reaching through the Genome, In: Perspectives on Properties of the Human Genome Project; Kieff, F. Scott Ed. Amsterdam, 2003; 209, 225 who argues that legal provision of reach-through rights should follow indications in the market that such allo-

include all potential pharmaceutical candidate compounds identified by assaying, the issue was examined in the course of a trilateral study in 2001.[698] In this case, the patent offices agreed not to accept claims reaching beyond that embodied by the patent. Applying those principles, the USPTO refused to grant the claim at issue. The hypothetical claim to compounds which bind to the receptor is rejected, since the applicant only discloses the function of the ligand without revealing information regarding its structure. Hence, the office is relatively tolerant with regard to the obviousness and utility criterion, but applies a particularly strict written description requirement. Relying on the principles developed in the *Regents' of California*[699] and *Enzo*[700] cases, the office supports a separate written description requirement.[701] The importance of the discussion, however, is attenuated by the fact that the claim at issue is also rejected due to a lack of enablement. When a skilled person is unable to make and use the invention without undue experimentation, the 'how-to-make' and 'how-to-use' prongs are not met. In sum, reach-through claims are subject to the same standards as all patent claims. An invigorated written description requirement generates a high threshold level to the granting of reach-through claims. With the USPTO also refusing to grant reach-through claims because of a lack of enablement, the dispute as to where to set the limits of a written description obligation is, however, not dispositive.

The EPO analysis is in accordance with German patent law developed in the field of chemicals. In the *Trioxan*[702] decision, the German Federal Supreme Court held that an unambiguous identification of the patented subject matter is the factual basis for not only the grant of the patent requirement but also for the start of the examination procedure made by the patent offices. The court discusses the first issue by analyzing how to reward the inventor appropriately on the one hand, and provide sufficient legal certainty on the other. Rewarding the inventor appropriately means, however, the court stated, that an inventor should only receive the advantages of a patent

cations are appropriate; also Kunin, Stephen G/ Nagumo, Mark/ Stanton, Brinaet al., Reach-through claims in the age of biotechnology, 51 American University Law Review April 2002, 609, provides a good overview how reach-through claims are treated by the USPTO applying the B3b Trilateral Study on reach-through claims undertaken by the Patent offices of Japan, the U.S. and Europe. Clark, Vici, Reach-through infringement: what are the limits? 6 Bio-Science Law Review 2000/2001, 249-252 who gives an overview about the legal situation in the U.K. For a comparative treatment, see OECD, Genetic Inventions, Intellectual Property Rights and Licensing Practices, Paris 2002, 63.

698 Trilateral Project B3b Comparative study on "reach-through claims", San Francisco, California, USA 2001.

699 Regents of the University of California v. Eli Lilly & Co., 119 F.3d 1559 (Fed. Cir. 1997).

700 Enzo Biochem v. Gen-Probe, 323 F.3d 956 (Fed. Cir. 2002).

701 Rochester illustrated how courts treat reach-through claims that have already been issued by the USPTO. The patent involving reach-through claims was based on the identification of molecules and processes in Cox-2 pathway. The claims to unidentified COX-2 inhibitors such as Celebrex were held to be invalid; See University of Rochester v. G.D. Searle & Co.; Inc, 358 F.3d 916 (Fed. Cir. 2004).

702 BGH, 3 IIC 226 (1972) – Trioxane.

if he discloses a new technical teaching to the public. The teaching of a substance invention under German law consists of making a substance available and providing at least one way to prepare it. Applying these principles to the claim at issue, the claim to the identified compounds of an *in-silico* method lacks both requirements and thus no "reward" can be provided to the inventor. With regard to unambiguous identification, the court in *Trioxane* emphasized that a claim must be drafted so precisely that it clearly demonstrates which substances are included in the claim language. Patent offices must be enabled to determine whether a substance already belongs to the prior art or not. Again, the principles established in *Trioxane* apply: if a substance is not described by its structural formula, any parameter that enables a clear distinction is sufficient for description. Claim language as "identified through …" does not provide such a distinction. Thus, it does not meet the standards for patentability.[703]

bb) Reach-through licensing

Another approach to protecting pharmaceutical inventions, instead of by broad reach-through claims is by reach-through licensing. The basic idea of this contract strategy is that the patent holder restricts access to his patented screening technology to those who agree to share future drug sales with him in the form of royalties. The specific characteristics of such royalties may violate existing anti-trust laws. The question of whether they are allowed influences the drafting of licensing contracts but also the amount of damage awards that can be claimed in the course of the infringement process. On the one hand, critics may claim that reach-through practices excessively reward those who rest on their laurels at the expense of those who carry research forward. On the other hand, it may be seen as a valuable way to allow early innovators to realize that their discoveries contribute to subsequent research. Whether the statutory background and existing case law is allowing the practice of reach-through licensing, will be discussed below.

i. Statutory background in Germany

A patent establishes a monopoly position that is authorized by legislation. If the patentee extends such a position by drafting personal licensing agreements that go beyond what is allowed by patent law, existing antitrust law rules may be violated. In order to prevent the monopoly right provided for the patentee from being extended beyond its legislative limitations by licensing contracts, the German competi-

703 Wolfram, Markus, 'Reach-Through Claims' and 'Reach-Through Licensing' - Wie weit kann Patentschutz auf biotechnologische Research Tools reichen?, Mitteilungen der deutschen Patentanwälte 2003, 57, 60; BGH, 3 IIC 226 (1972) – Trioxane.

tion law restricts the freedom of contract. Sections 17 and 18 of the Act of restraints of competition (ARC)[704] state that licensing agreements for the sale or use of certain intellectual property rights shall only contain such restrictions on the licensee that are covered by the scope of the intellectual property right as such. According to Section 17 para 1 sentence 2 ARC, only restrictions pertaining to the nature, extent, field of use, quantity, territory or duration of the right of use are allowed. The share of future profits is not addressed by this provision, which is why reach-through royalties are not covered. Reach-through royalties may, however, qualify for an exemption under Section 17 para 3 ARC if the licensee's economic freedom of movement or the market competition is "not unfairly restricted and if competition on the market is not substantially impaired because of the extent of the restrictions." In the event that research tools are used for identifying substances, the licensee will typically apply for a patent in order to protect such substances. During the duration of the patent, the substances are excluded from market competition. If no competition exists, an agreement regarding reach-through royalties does not thereby establish any restraint on the market. Furthermore, if the freedom of movement of the licensee is not restricted, an exemption will be granted. This is typically the case when parties agree upon moderate royalties. The exemption is considered to be granted if the cartel office does not reject the application within a period of three months.[705]

Another approach for protecting pharmaceutical inventions is through "milestone payments". In order to save the share of future profits, the parties agree upon payments triggered by contractual achievements. Typically, they are directed to major project events such as the beginning of pre-clinical or clinical trials or the achievement of drug approval. Milestone payments can be understood as escrows[706] and thus are acceptable under antitrust laws.[707]

ii. Legal situation under U.S. law

In the U.S., the topic of reach-through licensing is subject to heated discussion. The National Institutes of Health (NIH) rejects the idea of reach-through royalties due to policy reasons. It is claimed that they restraint research and the distribution of research tools. Only in exceptional cases are receivers of NIH subsidies allowed to conclude reach-through-licensing agreements.[708]

704 "Gesetz gegen Wettbewerbsbeschränkungen"

705 Kraßer, Rudolf, Patentrecht: Ein Lehr- und Handbuch zum deutschen Patent- und Gebrauchsmusterrecht, europäischen und internationalen Patentrecht, 5. Aufl., München 2004, 981.

706 "Aufschiebend bedingte Verpflichtung zur Zahlung einer Pauschallizenzgebühr für die Benutzung des Research tools"

707 Wolfram, Markus, 'Reach-Through Claims' and 'Reach-Through licensing' - Wie weit kann Patentschutz auf biotechnologische Research Tools reichen?, Mitteilungen der deutschen Patentanwälte 2003, 57, 63.

708 Department of Health and Human Services/National Institutions of Health: "Principles and Guidelines for Recipients of NIH Research Grants and Contracts on Obtaining and Dissemi-

Licenses providing reach-through royalties may give rise to antitrust issues under the patent misuse doctrine.[709] The doctrine requires that the alleged infringer demonstrate that the patent owner has unlawfully broadened the scope of the patent with a resulting anti-competitive effect. In *Zenith Radio Corp. v. Hazeltine Research, Inc.*, the Court of Appeals held that patent misuse is established if the grant of a patent license is conditioned upon payment of royalties on products, which do not involve the teaching of the patent.[710] The patentee "extend(s) the monopoly of his patent to derive a benefit not attributable to use of the patent's teachings" if "the leverage of a patent" is used to "garner as royalties a percentage share of the licensee's receipts from sales of other products.[711] Patent misuse thus must be assessed if the patentee's actions affect competition in unpatented goods or otherwise extends the economic effect beyond the scope of the patent grant.[712] There are several cases which deal with the question of whether reach-through royalties are considered to be patent misuse.

In *Sibia Neuroscience, Inc. v. Cadus Pharm. Corp.,* the infringing activity consisted of the use of a patented screening method to detect antagonists[713] and agonists[714] of proteins. The district court for the Southern District of California assessed damages, based on the calculation of a "reasonable royalty" of $18 million. The amount was calculated with the assumption that the parties had agreed upon reach-through royalties. With the subsequent invalidation of the patent by the CAFC due to obviousness in the light of the prior art[715], this type of damage assessment was not further examined. In *Ajinomoto Co. v. Archer Daniels Midland*, the claim was directed to methods of producing bacteria to make amino acids. The district court assessed damage awards by determining a royalty of $1.23/kg of amino acid sold. With the parties not disputing this calculation, it was not subject to any further discussion.[716] In addition, the decision of *Bayer v. Housey* assists in dealing with the details of patent misuse. In the district court decision, the court found that the plaintiffs sufficiently stated a claim of patent misuse reasoning that

nating Biomedical Research Resources, Final Notice", U.S. Federal Register Notice 64 FR 72090, 23.12.1999, http://ott.od.nih.gov/pdfs/64FR28205.pdf, last checked on January 21, 2008.

709 For a comparative analyis of the patent misuse doctrine see Riziotis, Dimitrios, Patent Misuse als Schnittstelle zwischen Patentrecht und Kartellrecht, GRURInt. 2004, 367.

710 Zenith Radio Corp. V. Hazeltine Research, Inc., 395 U.S. 100, 135. (Fed. Cir. 1969).

711 Zenith Radio Corp. V. Hazeltine Research, Inc., 395 U.S. 100, 136.

712 See C.R. Bard, Inc. v. M3 Sys., Inc., 157 F.3d 1340, 1372 (Fed. Cir. 1998).

713 An antagonist is a substance that attenuates the effects of an agonist by binding to the agonist's binding sites. See glossary, available at http://www.adrenoceptor.com/abc.htm, last checked on January 21, 2008.

714 An agonist is a substance that binds to a receptor and activates it, producing a pharmacological response (such as contraction, relaxation, secretion, enzyme activation, etc.), see glossary, available at http://www.adrenoceptor.com/abc.htm, last checked on January 21, 2008.

715 Sibia Neuroscience, Inc. v. Cadus Pharm. Corp.225 F.3d 1349 (Fed. Cir. 2000).

716 The CAFC in Ajinomoto Co. v. ADM Co., 228 F.3d 1338 held that the claims at issue were valid and infringed by a commercial process using bacteria made by these methods.

> "Certain practices that do not equal *per se* patent misuse may constitute misuse if a court determines that such practices do not reasonably relate to the subject matter within the scope of the patent claims. If "the practice has the effect of extending the patentee's statutory rights and does so with an anti-competitive effect, ... the finder of fact must decide whether the questioned practice imposes an unreasonable restraint on competition".[717]

For the reasons set forth above, the legal treatment of reach-licensing agreements is yet not clear. Hence, it is advisable to handle such strategy with caution.

IV. Conclusion

Based on the study of the different approaches provided by the European and the U.S. patent offices, it can be concluded that both offices largely share the same views with respect to the patentability requirements of 3-D protein structures-related claims.[718] Yet, different approaches exist with regard to the patentability of *in-silico* screening methods. The European Patent office accepts the claim, assuming a patentable subject matter due to a further technical effect of the computerized invention. The USPTO, by contrast, rejects the claim, concluding there is obviousness due to the understanding that the algorithm is considered as non-functional descriptive material.

The study shows that an inventor seeking patent protection for 3-D protein structures should obey the following guidelines.[719] Generally, a patent applicant should provide accurate and precise information regarding the 3-D structural coordinates. Furthermore, a precise description of how the structural analysis was carried out should be provided in the patent specification. Isolated and determined 3-D protein structures establish novelty, if the inventor proves that the tertiary structure coordinates are a more unambiguous parameter than the amino acid sequence already disclosed in the prior art.

The further rule that novelty can be derived from physical morphology applies principles developed in the field of chemical inventions. The possibility of creating novelty through the principles of selection inventions are also in line with classical chemical patent principles. The question of dependency from the patent covering the whole protein is another key factor and will be discussed below.

717 Bayer v. Housey, 169 F.Supp.2d 328, 331 (District Court of Deleware 2001).

718 European Patent Office, Japan Patent Office, United States Patent and Trademark Office, Trilateral Project WM4, Comparative Studies in New Technologies (Biotechnology, Business Methods, etc.), Report on Comparative Study on Protein 3-Dimensional (3-D) Structure Related Claims, Vienna 2002, 32; also Vinarov, Sara D., Patent protection for structural genomics-related inventions, Journal of structural and functional genomics 2003, 191, 206.

719 Vinarov, Sara D., Patent protection for structural genomics-related inventions, Journal of structural and functional genomics 2003, 191, 207, who emphasizes that understanding how patent offices will analyze structural genomics-based inventions is crucial for formulating strategies in patent prosecution and litigation.

As for proteomics claims in the field of bioinformatics, principles from both computer-implemented inventions and inventions involving biological material should apply. Therefore, the author suggests that a further technical effect, as well as the acknowledgement of functional descriptive material, may be derived from the biological function the protein performs *in-vivo*.

As for compounds screened by *in-silico* methods, the strategy to draft reach-through claims should be handled with caution. With strict conditions set out for the written description/sufficient disclosure requirement and enablement factor, it may be advisable to use other approaches such as milestone payments or reach-through licensing methods. As long as the claim defines the identified compound by size and shape, it is not considered a reach-through claim. In order to meet the patentability requirements of written description/sufficient disclosure and enablement, it is advisable for applicants to disclose theoretical information about the size and shape of binding sites within the computerized method and in responding compounds. Inventors, however, must take into account that such claims involve a high risk that they will be rendered invalid. Even if only one prior art ligand has the shape and size demonstrated by the claim and would therefore respond to the *in-silico* protein, the claim lacks novelty. With many molecules being reported in prior art, but not all of them defined by size and shape, the concrete risk of a destruction of novelty is difficult to assess.[720]

Finally, it must again be emphasized that the patentability of 3-D protein structure is a key factor in the treatment of a number of frequently occurring neurodegenerative disorders. With the increased aging of society, Alzheimer's, one of the diseases based on amyloid brain plaques, is increasingly reported worldwide. Prion-based diseases, such as BSE or CJD, accompany industrial developments such as intensive mass animal farming.[721] In view of these diseases, there clearly is a need for cost-effective drugs related to the treatment of prion diseases. Because the tertiary folding stage of the infectious proteins is the major cause of this diseases, effective treatment must be based on knowledge of their 3-D structure. Research must specifically emphasize the visualization of the structural transition from the normal, cellular prion, Prp C to the diseased form, Prp Sc. As yet, the understanding of the structural biology of the pathogenic conversion, however, remains incomplete in many

720 Eisenberg, Rebecca S., Reaching through the Genome, In: Perspectives on Properties of the Human Genome Project; Kieff, F. Scott, ed. Amsterdam 2003; 209, 225.

721 A major risk for the development of CJD is the treatment with growth hormones. Two doctors in France were charged with involuntary manslaughter of a child who had been treated with growth hormones derived from corpses. The child contracted Creutzfeldt-Jakob Disease. According to French studies, there have been 24 reported cases of CJD in children who had been subject of growth hormone treatments between 1983 and mid-1985. Fifteen of these persons have died. It now appears possible that hundreds of children in France have been treated with growth hormone derived from dead bodies at the risk of contracting CID; see U.S. Patent 6916419 "Device for Removal of Prions from Blood, Plasma and other Liquids" by Prusiner, Stanley B./Safar, Jiri G., Oakland, CA 2005.

ways.[722] There exist a large number of patents related to prions.[723]Inventions range from methods related to the modification[724] and detection[725] of prions or models of prion diseases[726], to methods related to antibodies[727] or devices for removal of prions from blood, plasma and other liquids.[728] Only recently, have scientists developed an artificial protein that can trigger a neurological disorder similar to BSE. They produced a normal prion protein fragment in bacteria and folded it into larger, abnormally shaped structures. These structures were then injected into the brains of mice. The animals began to show symptoms similar to those occurring in BSE.[729] Hence, the field of prion research plays a crucial role in the proteomic era and it can be expected that a plurality of patent applications will be filed in the near future. In view of the importance of these technologies, the patent law systems must provide adequate protection. Since the tertiary stage is the crucial element, this protection is only achieved if the 3-D structure is sufficient to create novelty, irrespective of whether the primary sequence of the protein is already included in the prior art.

722 For example, it is unknown exactly which structural regions of PrP C bear the crucial properties for the conformational change to occur. It is also not disclosed which regions of PrP Sc bear the infectious properties; see U.S. Patent 6916419, "Device for Removal of Prions from Blood, Plasma and other Liquids" by Prusiner, Stanley B./Safar, Jiri G., Oakland, CA 2005.

723 The Nobel laureate Stanley B. Prusiner has been involved in the development of at least 40 patents granted in between 1996 and 2005, available at http://patft.uspto.gov/, last checked on January 21, 2008.

724 International Patent Application WO/2002/049460 "Method for modifying the protein structure of prions PrP in a targeted manner" by Kortschak, Fritz, Berlin 2003.

725 U.S. Patent 7208281 „Ligands used for detecting prions" by Kiesewetter, Holger/Salamar, Abdulgabar, Berlin 2003.

726 U.S. Patent 6767712 "Models of prion disease" by Prusiner, Stanley B./Carsten, Korth, Oakland, CA 2004.

727 U.S. Patent 6858397, PrusinerAntibodies specific for native PrPsc by Stanley B/Williamson, R. Anthony/Burton, Dennis R., Oakland; La Jolla 2005.

728 U.S. Patent 6916419 "Device for Removal of Prions from Blood, Plasma and other Liquids" by Prusiner, Stanley B./Safar, Jiri G Oakland, CA 2005.

729 See BBC News from July 30, 2004, available at: http://news.bbc.co.uk/go/pr/fr/-/1/hi/health/3936519.stm, last checked on August 1, 2005.

Chapter 4: Scope of Protection

A. Introductory Remarks

Patent law should strike a reasonable balance between the competitive concerns of open access and exclusivity. Open access can facilitate knowledge distribution and collaboration in advancing science. Exclusivity can ensure interest and financial investment in scientific research and development.[730] When the first DNA sequence patents were granted, a lively debate about their adverse effect on research and development emerged. The debate climaxed when the NIH filed a patent application, which included an enormous number of cDNA without any indication of function.[731] Although the USPTO finally rejected the NIH application, existing concerns persisted.[732] Specifically, several observers raised the question of whether future innovations related to a certain protein structure could potentially infringe existing DNA claims. In this case, it was argued, R&D expenditures by companies that do not possess any cDNA patents could be severely limited, thus leading to an undersupply of innovative capacity.[733]

The issue was regarded particularly pressing because at the time of the first DNA patents, it was not understood how the now abundant genetic information could be transformed into medical and pharmaceutical applications. In particular, many researchers expected that genetic information would be used quite directly in medical treatments, for example in the form of gene therapies.[734] Others, however, hypothesized that other aspects of the encoded protein, for example its tertiary structure, would have to be identified first. Given this information, it would then be possible to develop sensible therapies. In this situation, however, a DNA patent with a very broad scope would likely be detrimental to a dynamic biotechnological progress. Consequently, the question of whether the scope of protection of DNA patents would provoke infringements by (yet unrealized) proteomic inventions was discussed intensively.[735] On the one hand, the idea of allowing a company to patent a genetic sequence that has been around since the beginning of life was perceived as

730 Sung, Lawrence M., Patenting nonassociated polymeric structures (NAPS): implications for structural genomic data release, 4 Journal of Structural Functional Genomics 2003, 211, 211.

731 Straus, Joseph, Abhängigkeit bei Patenten auf genetische Information - ein Sonderfall, GRUR 1998, 314, 314.

732 See Chapter 3 A II 2 a.

733 Widge, Alik, Patent Pending: A Primer on Gene Patents, Pittsburgh 2003, 3-4; available at http://www.amsa.org/pdf/genepatents.pdf, last checked on January 21, 2008.

734 Widge, Alik, Patent Pending: A Primer on Gene Patents, Pittsburgh 2003, 4, available at http://www.amsa.org/pdf/genepatents.pdf, last checked on January 21, 2008.

735 Service, Robert F., Gene and Protein patents get ready to go head to head, 294 Science 2001, 2082.

moderately alarming. On the other hand, the design of new gene-based pharmaceuticals in the U.S. requires years of commitment and immense capital investments. Without the ability to receive protection, companies would have no means of recovering the costs of their investments and innovation would be blocked.[736]

With genetic patent holders typically owning exclusive rights to the recombinant produced protein, basic conflicts between 3-D related claims and DNA patents are expected to emerge. However, a detailed examination of potential conflicts may also reveal that their relevance is limited, and that the patent system does strike an appropriate balance between open access and exclusivity. In the end, the issue is reduced to a thorough analysis of claim construction regarding both literal and equivalent infringement. The following chapters attempt to provide such an analysis, focusing on the scope of 3-D protein structure related claims. First, general aspects of claim construction and its relation to the scope of protection of biotechnological inventions will be discussed. Second, chapter IV. C. seeks to explore the scope of recombinant protein claims with regard to infringement through the use of 3-D protein structures.

B. Claim construction in the U.S. and in Europe

I. Claim construction and doctrine of equivalents in the U.S.

1. Claim Construction

In the U.S., the determination of infringement depends in the first place on claim construction.[737] In case of a conflict, the court must interpret whether or not a used product/process falls within what is covered by the patent scope.[738] The Federal Cir-

736 Fernandez, Dennis/Chow, Mary, Intellectual Property Strategy in Bioinformatics and Biochips, Journal of Patent and Trademark Office Society June 2003, 465, 466.

737 NTP, Inc. v. Research In Motion, Ltd., 418 F.3d 1282 (Fed. Cir. 2005) ("Claim construction is a matter of resolution of disputed meanings and technical scope, to clarify and when necessary to explain what the patentee covered by the claims, for use in the determination of infringement" [citation omitted]); Sarnoff, Joshua, The Doctrine of Equivalents and Claiming the Future after Festo, 14 The Federal Circuit Bar Journal 2004, 403, 404.

738 35 U.S.C. Section 271 (a) states: "Except as otherwise provided in this title, whoever without authority makes, uses, offers to sell, or sells any patented invention during the term of the patent therefor, infringes the patent." As for the infringement of process patents, Section 271 (g) U.S.C. provides that: "Whoever without authority imports into the United States or offers to sell, sells, or uses within the United States a product, which is made by a process patented in the United States shall be liable as an infringer, if the importation, offer to sell, sale, or use of the product occurs during the term of such process patent. In an action of infringement of a process patent, no remedy may be granted for infringement on account of the noncommercial use or retail sale of a product unless there is no adequate remedy under this title for infringement on account of the importation or other use, offer to sell, or sale of that product. A product which is made by a patented process will, for purposes of this title, not be considered

cuit has characterized claim construction as "the central issue of every patent appeal".[739] Indeed, since the decision in *Markman v. Westview Instruments, Inc*.[740], it has taken on paramount significance, often of case-dispositive nature. In *Markman I*, the Federal Circuit (en banc) ruled that "the interpretation and construction of patent claims, which determine the scope of the actual patent right, is a matter of law exclusively for the court."[741] In *Markman II,* the Supreme Court decided that claim construction was an issue for the judge rather than the jury.[742] Furthermore, the Supreme Court affirmed *Markman I,* stating that claims must be compared with the accused product or process in order to determine whether each limitation of the claim is met, either literally or under the doctrine of equivalents. Claim construction must be handled carefully, since any mistake can distort the entire infringement analysis.[743] After *Markman II*, the Federal Circuit stated that claim construction is purely a matter of law with no underlying or subsidiary issues of fact.[744] Hence, the Federal Circuit reviewed a district court's reasoning regarding claim construction without deference. Claim construction therefore is a question of law, which is reviewed *de novo* on appeal, "including any allegedly fact-based questions that are presented".[745]

Patent claims must be construed "objectively and without reference to the accused device.[746] A court first evaluates the intrinsic evidence, such as the patent itself, its claims, written description, and the prosecution history. As for the prosecution history, all relevant arguments made which are included in the specification must be considered.[747] The starting point for ascertaining the meaning of a patent claim is its language. In general, terms in a patent claim are given their ordinary meaning to one of ordinary skill in the relevant art. The meaning of a claim term is as it would be

to be so made after (1) it is materially changed by subsequent processes; or (2) it becomes a trivial and nonessential component of another product."

739 Sulzer Textil v. Picanol, 358 F.3d 1356, 1366 (Fed. Cir. 2004); Minco v. Combustion Engineering, 95 F.3d 1109, 1114 (Fed. Cir. 1996).

740 Markman vs. Westview Instruments, Inc., 52 F.3d 967 (Fed. Cir. 1995) (en banc). ("Markman I"), affirmed in 517 U.S. 370 (1996) ("Markman II") (claim construction is an issue for the judge rather than the jury)

741 Markman I, 52 F.3d 967, 977.

742 Markman II, 517 U.S. 370, 391(1996).

743 Markman II, 517 U.S. 370 at 370. See also Weiss, Robert C./Miller Todd R., Practical tips enforcing and defending patents, 85 Journal of the Patent and Trademark Office Society 2003, 791, 793.

744 Cybor, 138 F.3d, 1448 (Fed. Cir. 1998)

745 Cybor, 138 F.3d, 1448, 1455 ("[The Supreme] Court held that the totality of claim construction is a legal question to be decided by the judge."), also Weiss, Robert C./Miller Todd R, Practical tips enforcing and defending patents, 85 Journal of the Patent and Trademark Office Society 2003, 791, 794.

746 Vivid Tech., 200 F.3d, 795, 803 (Fed. Cir. 1999) ("[T]hose terms need to be construed that are in controversy").

747 Depuy Spine, Inc. v. Medtronic Sofamor Danek, Inc., 469 F.3d 1005, 1014 (Fed. Cir. 2006) ("In determining the meaning of the disputed claim limitation, court looks principally to the intrinsic evidence of record, examining the patent claim language itself, the written description, and the prosecution history, if in evidence.")

interpreted by one skilled in the art, until clear evidence is provided that proves that the inventor intended a different meaning. In order to determine what the ordinary meaning is, a court may rely on general and technical dictionary definitions.[748] In addition to such "intrinsic" evidence, the court may also use "extrinsic evidence", such as treatises, inventor testimony, dictionary definitions, and expert testimony to interpret patent claims to determine the meaning of the claims to a person having ordinary skill in the art.[749] The extent to which one should rely on such evidence, rather than intrinsic evidence in the specification and prosecution history is largely in dispute. In *Phillips v. AWH Corp.*,[750] the CAFC thoroughly discussed the limitations of extrinsic evidence. The Court explained that "[extrinsic evidence] is unlikely to result in a reliable interpretation of patent claim scope unless considered in the context of the intrinsic evidence."[751] Nevertheless, the court emphasized that "… extrinsic evidence can help educate the court regarding the field of the invention and can help the court determine what a person of ordinary skill in the art would understand claim terms to mean".[752] In summary, courts rarely rely on inventor testimony regarding meaning, both because of the obvious interest of the inventor and because the inventor's meaning is not directly relevant to the understanding of the person skilled in the art.[753] Hence, claim construction presupposes the consideration of various elements, such as used terms, the definition provided in the specification, the prosecution history, arguments made by the applicant, the disclosure of the prior art, and knowledge of those skilled in the relevant art. Further extrinsic evidences include treatises or inventor and expert testimony.[754]

748 Phillips v. AWH Corp., 415 F.3d 1303 (Fed. Cir. 2005) (en banc) ("[R]ecourse to the specification is limited to determining whether the specification excludes one of the meanings derived from the dictionary, whether the presumption in favor of the dictionary definition of the claim term has been overcome by an explicit definition of the term different from its ordinary meaning or whether the inventor has disavowed or disclaimed scope of coverage, by using words or expressions of manifest exclusion or restriction, representing a clear disavowal of claim scope." citation omitted); Weiss, Robert C./Miller Todd R , Practical tips enforcing and defending patents, 85 Journal of the Patent and Trademark Office Society 2003, 791, 800f.

749 Panduit Corp. v. HellermannTyton Corp., 451 F.3d 819, 827 (Fed. Cir. 2006) ("However, if the language of the contract is ambiguous, then the court may consider extrinsic evidence to determine the intent of the parties.")

750 Phillips v. AWH Corp., 415F.3d 1303, 1313 (Fed. Cir. 2005)(en banc)

751 Phillips v. AWH Corp, 415F.3d 1303, 1313.

752 Phillips v. AWH Corp, 415F.3d 1303, 1313.

753 Weiss, Robert C./Miller Todd R., Practical tips enforcing and defending patents, 85 Journal of the Patent and Trademark Office Society 2003, 791, 809.

754 Vitronics Corp. v. Conceptronic, Inc., 90 F.3d 1576, 1584 (Fed. Cir. 1996) ("Only if there were still some genuine ambiguity in the claims, after consideration of all available intrinsic evidence, should the trial court have resorted to extrinsic evidence, such as expert testimony"); Weiss, Robert C./Miller Todd R., Practical tips enforcing and defending patents, 85 Journal of the Patent and Trademark Office Society 2003, 791, 800. Since Vitronics, the District court became more lenient, see Pitney Bowes, 182 F.3d 1298, 1309 (Fed. Cir. 1999) ("[I]t is entirely appropriate, perhaps even preferable, for a court to consult trustworthy extrinsic evidence to ensure that the claim construction it is tending to from the patent file is

After the claim has been construed, the second step of claim construction requires that every element in each asserted claim must be compared to the accused product or process. If each element is found in the product or process being used, literal infringement is established. This is often called the "all-elements" rule.[755] In sum, the patent claims, understood by a person skilled in the art, are the decisive element of claim construction. Furthermore, patent files can be used to interpret the claims and this interpretation is made from the time of infringement.[756]

2. Doctrine of equivalents

If literal infringement is not established, the patent may still be infringed under the doctrine of equivalents according to which "[t]he scope of the patent is not limited to its literal terms but instead embraces all equivalents to the claims described."[757] The idea of extending claims beyond their literal meaning had been addressed in early U.S. case law.[758] In the decision *Winans v. Denmead*[759], the Supreme Court ruled on three major points, stating that "specifications are to be construed liberally" and the terms "cylindrical and conical" are to cover "octagonal and pyramidal".[760] In *Sanitary Refrigerator Co. v. Winters*,[761] the Supreme Court further determined that the "Triple Identity Test" or "function-way-result-test" were an appropriate means for defining equivalents. Pursuant to this method, equivalents exists if a product "performs substantially the same function in substantially the same way to obtain the same result".[762] The applicable principle is that "if two devices do the same work in substantially the same way, and accomplish substantially the same result, they are the same, even though they differ in name, form or shape".[763] In *Graver Tank*[764], the

not inconsistent with clearly expressed, plainly apposite, and widely held understandings in the pertinent technical field.").

755 Depuy Spine, Inc. v. Medtronic Sofamor Danek, Inc., 469 F.3d 1005 (Fed. Cir. 2006).

756 Warner-Jenkinson v. Hilton Davis, 520, U.S. 17 (1997); W.E. Hall Co., Inc. v. Atlanta Corrugating, 370 F.3d 1343, 1353 (Fed. Cir. 2004).

757 Doctrine of Equivalents defined in Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co., 535 U.S. 722 (2002) (Festo VIII). The doctrine was first adopted in Winans v. Denmead, 56 U.S. 330 (1854) and further developed in Graver Tank v. Linde, 339 U.S. 605, (1950) and Warner-Jenkinson v. Hilton Davis, 520 U.S. 17 (1997). The "Festo Litigation" is of major importance for what is considered equivalent, see below at footnotes 767, 780ff.

758 Goodyear Dental Vulcanite Co. V. Davies, 102 U.S. 222, 228 (1880); Bergen-Babinecz, Katja/Hinrichs, Nikolaus/Jung, Roland/Kolb, Georg, Zum Schutzbereich von US-Patenten: Festo und eine deutsche Sicht, GRURInt. 2003, 487, 490.

759 Winans v. Denmead, 56 U.S. 330 (1854); Chisum, Donald, Chisum on Patents, Volume 5A, § 18.02[1], stating "Winans v. Denmead (1853) was the first decision to use the doctrine of equivalents to do serious damage to the literal meaning of the language of a patent claim."

760 Winans v. Denmead, 56 U.S. 330, 341, 332.

761 Sanitary Refrigerator Co. v. Winters, 280 U.S. 3 (1929).

762 Sanitary Refrigerator Co. v. Winters, 280 U.S. 30, 42, 50.

763 Union Paper-Bag Machine Co. v. Murphy, 97 U.S. 120 (1877).

Supreme Court made a further statement, ruling that an alternative method for determining equivalents is the 'insubstantiality of differences test'. The question that emerges in the context of this method is whether persons reasonably skilled in the art would have known of the interchangeability of an ingredient not contained in the patent with one that was.[765] The 'modern' doctrine of equivalents has been substantially characterized by the more recent '*Festo*-litigation'.[766] Since *Festo* primarily focuses on limitations of the doctrine rather than its pre-conditions, these decisions are illustrated below.[767]

The reach of non-literal infringement is restrained by a number of legal tenets, such as the "all elements" rule, the prior art, public dedication, and the doctrine of prosecution history estoppel. The "all elements-rule" requires that equivalency exists only for an accused product or process that contains all of the limitations of a claim, either literally or equivalently. Thus, a skilled artesan must examine the doctrine of equivalents element by element. In the event of a missing element, there is no infringement unless an equivalent for this missing element exists.[768] In *Warner-Jenkinson*[769], the Supreme Court stated in this context:

> "It is important to ensure that the application of the doctrine, even as to an individual element, is not allowed such broad play as to effectively eliminate that element in its entirety."[770]

Hence, the all-elements rule sets the level of generality of the invention at which equivalents and a literal presence are to be determined. *Warner-Jenkison*, however, fails to explain what constitutes an "element" or limitation that sets that level.

The restraint of non-literal infringement by the prior art rule has been established in *Wilson*[771], where the Federal Circuit ruled that

764 Graver Tank v. Linde Air Products Co., 339 U.S. 605 (1950), see also Bergen-Babinecz, Katja/Hinrichs, Nikolaus/Jung, Roland/Kolb, Georg, Zum Schutzbereich von US-Patenten: Festo und eine deutsche Sicht, GRURInt. 2003, 487, 488.

765 Graver Tank v. Linde Air Products Co., 339 U.S. 605 at 609; some parts of literature follow the view that the 'function-way-result' test must be conducted in the course of the 'insubstantiality of differences test', see Bergen-Babinecz, Katja/Hinrichs, Nikolaus/Jung, Roland/Kolb, Georg, Zum Schutzbereich von US-Patenten: Festo und eine deutsche Sicht, GRURInt. 2003, 487, 488.

766 The Festo litigation started in 1994 when the District Court for the District of Massachusetts held that Shoketsu had infringed patents belonging, the Festo company under the doctrine of equivalents; see Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co., 1994 WL 1743984 (D.Mass 1994) (Festo I). With regard to this 'modern' doctrine of equivalents, see Sarnoff, Joshua, The Doctrine of Equivalents and Claiming the Future after Festo, 14 The Federal Circuit Bar Journal 2004, 403.

767 See end of same subchapter, Chapter 4 B I 2.

768 Depuy Spine, Inc. v. Medtronic Sofamor Danek, Inc., 469 F.3d 1005, 1016 (Fed. Cir. 2006). („Each element contained in a patent claim is deemed material to defining the scope of the patented invention, and thus the doctrine of equivalents must be applied to individual elements of the claim, not to the invention as a whole.").

769 Warner-Jenkinson v. Hilton Davis, 520 U.S. 17 (1997).

770 Warner-Jenkinson v. Hilton Davis, 520 U.S. 17, 29.

771 Wilson Sporting Goods Co. v. David Geoffrey & Assoc., 904 F.2d 677 (Fed. Cir. 1990)

> "a patentee should not be able to obtain, under the doctrine of equivalents, coverage which he could not lawfully have obtained from the PTO by literal claims … since prior art always limits what an inventor could have claimed, it limits the range of permissible equivalents of a claim."[772]

As a possible test for the prior art limitation of equivalents, the court evaluated the construction of a hypothetical claim literally, including the asserted equivalent, and tested whether its scope was permissible in the light of prior art. For the court such testing was preferable, since it "permits a more precise analysis than determining whether an accused product would have been obvious from the level of prior art".[773]

Pursuant to the public dedication rule, patentees who fail to claim predictable alternatives and draft claims more narrowly than what is disclosed by the provided written description cannot rely on the doctrine of equivalents.[774] Rejecting the application of the doctrine, Judge Rader in *Sage* concluded:

> "The claim at issue defines a relatively simple structural device. A skilled patent drafter would foresee the limiting potential of a [narrowly drawn structural limitation]. No subtlety of language or complexity of the technology, nor any subsequent change in the state of the art, such as later-developed technology, obfuscated the significance of this limitation at the time of its incorporation into the claim. If Sage desired broad patent protection …, it could have sought claims with fewer structural encumbrances… However, as between the patentee who had a clear opportunity to negotiate broader claims but did not do so, and the public at large, it is the patentee who must bear the cost of its failure to seek protection for this foreseeable alteration of its claimed structure."[775]

Pursuant to the Federal Circuit's decision in *Maxwell* a subject matter disclosed in the specification but not claimed is "dedicated to the public".[776] A patentee shall be prevented from filing narrow claims, avoiding examination of broader claims but seeking to extend the patent scope through the doctrine of equivalents.

A further key limitation on the scope of equivalents is the prosecution history.[777] This doctrine states that a patentee cannot recapture through equivalents what he has surrendered during patent prosecution. This rule has been substantially characterized by the above-mentioned '*Festo*-litigation'.[778]In the decision *Festo Corp. v. Shoketsu Kinyoku Kogyo Kabushiki Co*. (2002)[779], the Supreme Court reversed an *en banc* Federal Circuit decision[780] which had held that, if a claim is narrowed for any reason

772 Wilson Sporting Goods Co. v. David Geoffrey & Assoc., 904 F.2d 677, 684.
773 Wilson Sporting Goods Co. v. David Geoffrey & Assoc., 904 F.2d 677, 684. See also Sarnoff, Joshua, The Doctrine of Equivalents and Claiming the Future after Festo, 14 The Federal Circuit Bar Journal 2004, 403, 447.
774 Sage Prods., Inc. v. Devon Indus., Inc., 126 F.3d 1420, at 1424-25 (Fed. Cir. 1997).
775 Sage Prods., Inc. v. Devon Indus., Inc., 126 F.3d 1420, at 1420 (Fed. Cir. 1997), also Adelman, Martin J./Rader, Randall R./Thomas, John R./Wegner, Harold C., Cases and materials on patent law, St. Paul 2003, Chapter 15, Section 15.2.
776 Maxwell v. J. Baker Inc., 86 F.3d at 1106-1107 (Fed. Cir. 1996).
777 Geißler, Bernhard, Noch lebt die Äquivalenzlehre, GRURInt 2003, 1, 4-6.
778 See footnote 758.
779 Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co., 535 U.S. 722 (2002) (Festo VIII).
780 Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co., 234 F.3d 558, 564 (Fed. Cir. 2000) (en banc) (Festo VI).

related to patentability during prosecution, resorting to the doctrine of equivalents for the claim element at issue is totally barred ("complete bar" rule).[781]The Supreme Court ultimately adopted to a "flexible bar" approach under which even narrowed claims could still be entitled to some range of equivalents.[782] The Federal Circuit on remand determined, to some extent, the manner in which issues of prosecution history estoppel would be assessed.[783] All narrowing amendments made to comply with any provision of the patent laws give rise to a presumption that equivalents have been surrendered. This presumption, however, can be rebutted in various ways, each of which appears difficult to establish. The rebuttal examination is a legal issue for the judge to decide, even though it includes underlying factual issues. Legal practitioners frequently complain that the *Festo* litigation and the resulting rules of prosecution history estoppel have added a high degree of unpredictability to the doctrine of equivalents. The examination of what is considered an unacceptable diversion/narrowing amendment certainly depends on a case-by-case analysis and might often be difficult to predict. Applicants, however, know that if they surrender subject matter they might later have to suffer the most consequences. Hence, it is likely that most if not all applications will avoid surrender.[784]

In *Warner-Jenkinson*, the court also concluded that the time for determining equivalency is the time of infringement.[785] It must be emphasized that the question of whether equivalency exists is based on the post-issued/later-arising knowledge of technological interchangeability of elements. Thus, a product or process may be held equivalent if it encompasses a technological element either invented after the patent is issued or discovered to be a substitute after that time. This principle applies whenever the later-arising technological substitute was, or could have been, considered by the inventor as part of the invention, provided that the substituted element does not entirely negate the claimed limitation it does not represent. Consequently, the doctrine of equivalents expands the patent's scope over time.[786] Hence, the purpose of the U.S. doctrine of equivalents is principally to address the unforeseeable. A patent drafter must include every foreseeable application in his claim to anticipate how new technology would be applied in a fashion that every reasonable drafter of patent claims would also foresee.

781 Teague, Brian J., Festo and the Future of the Doctrine of Equivalents, 3 Journal of Intellectual Property 2004, 1-19, 3.

782 Festo VIII., 535 U.S. 722, 738 (2002).

783 Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co., No. 95-1066, 2003 WL 22220526 (Fed. Cir. 2003) (Festo IX).

784 Sarnoff, Joshua, The Doctrine of Equivalents and Claiming the Future after Festo, 14 The Federal Circuit Bar Journal 2004, 403, 430.

785 Warner-Jenkinson v. Hilton Davis, 520, U.S. 17, 19.

786 Sarnoff, Joshua, The Doctrine of Equivalents and Claiming the Future after Festo, 14 The Federal Circuit Bar Journal 2004, 403, 410.

II. Claim construction and Doctrine of equivalents under German law

1. Claim Construction

The core provisions for the interpretation of claims are Art. 69(1) EPC, and § 14 GPA, which state:

> The extent of the protection conferred by a European patent or a European patent application shall be determined by the terms of the claims. Nevertheless, the description and drawings shall be used to interpret the claims.

The rule is read in light of the Protocol on the Interpretation of Art. 69 of the Convention. Art. 1 of the Protocol states:

> "Art. 69 should not be interpreted in the sense that the extent of the protection conferred by a European patent is to be understood as that defined by the strict, literal meaning of the wording used in the claims, the description and drawings being employed only for the purpose of resolving an ambiguity found in the claims. Neither should it be interpreted in the sense that the claims serve only as a guideline and that the actual protection conferred may extend to what, from a consideration of the description and drawings by a person skilled in the art, the patentee has contemplated. On the contrary, it is to be interpreted as defining a position between these extremes which combines a fair protection for the patentee with a reasonable degree of certainty for third parties."

Thus, the first sentence deals with the interpretation of claims, ruling that claims should not be read literally and descriptions and drawings only serve the purpose of resolving any ambiguity existing in the claims. The second sentence does not refer to the interpretation of claims. It clarifies, rather, that one cannot go beyond the claims to what, on the basis of the specification and drawings, it appears that "the patentee has contemplated". Finally, the last sentence indicates that, in constructing the scope of protection according to the content of the claims but avoiding literalism, the courts of the contracting states should aim at "a fair protection for the patentee with a reasonable degree of certainty for third parties."[787]

An illustrative example of claim construction is provided by the earlier mentioned decision of Amgen/TKT[788], where the English House of Lords had to decide whether TKT's 'GA-Epo' (Dynepo), produced by a process called "gene activation", infringes Amgen's patent related to the recombinant 'Epo'.[789] The presentation of the decision is particularly useful in demonstrating the different steps of claim interpretation.[790] The process of TKT's gene activation involved the introduction of a nu-

787 Kirin-Amgen Inc v. Hoechst Marion Roussel, [2005] R.P.C. 9, 2004 WL 2330204, Meier-Beck, Peter, Aktuelle Fragen der Schutzbereichsbestimmung im deutschen und europäischen Patentrecht, GRUR 2003, 905, 905.

788 Kirin-Amgen Inc v. Hoechst Marion Roussel, [2005] R.P.C. 9, 2004 WL 2330204, see also Chapter III Part A 2 C (b). As for earlier decisions on the subjects see Welch, Andreas, Der Patentstreit um Erythropoietin , GRURInt. 2003, 579, 592.

789 Chapter 3 A II 3 a.

790 As remarked by Rüdiger Rogge, then presiding judge of the 10th (intellectual property) Senate of the Bundesgerichtshof, "decisions of other countries on the extent of protection af-

cleotide sequence into the genome of a human cell upstream of the erythropoietin gene. The nucleotide sequence "effectively overrode the regulator, which normally switched off the gene, and thus switched it on." TKT's cells contained endogenous erythropoietin DNA with respect to the coding regions, but also an exogenous promoter construct that was introduced upstream of that endogenous DNA.[791] Amgen's patent claimed the expression of erythropoietin in mammalian cells using DNA inserted in a hybrid vector of bacterial plasmid and viral genomic origins. Amgen only asserted the infringement of claim 19 and 26, since TKT did not produce any GA-erythropoietin in the United Kingdom and the alleged infringement was based on TKT's importation of 'GA-EPO'.[792] The critical issue the House of Lords had to discuss was whether a skilled person would classify "host cell" as meaning a cell which is host to the DNA sequence coding for 'Epo'.[793] A different understanding put forward by Amgen was that it can involve a sequence which is endogenous to the cell such as the human 'Epo' gene expressing 'GA-Epo', as long as the cell is host to some exogenous DNA. In the TKT method, such a cell hosts the "gene activation sequence".[794] As a first step, the judge interviewed a number of skilled persons as witnesses, all of whom said that they would have interpreted Claim 1 to be directed to a "DNA sequence coding for 'Epo' which had been isolated or synthesized and was suitable for expression in a host cell."[795] Furthermore, the judge relied on the language used in the patent description. The court concluded that the terms "for use in securing expression … of a polypeptide" refer to the DNA encoding for 'Epo' instead of the control sequence which "switches on" the expression of endogenous DNA. This interpretation, the judge reasoned, was supported by paragraph (b) of Claim 1, which broadened the claim to sequences that hybridized under stringent conditions to "the protein coding regions".[796] The judges therefore concluded that a person skilled in the art would not classify the endogenous coding sequence that expressed TKT's 'Epo' as falling within claim 1.[797] The Amgen/TKT decision shows that the issue of whether a patent claim can cover later-arising technologies is decided on the level of claim construction.

The patentable subject matter is understood objectively and does not depend on the subjective perception of the patentee. It is not the court's task to detect what the inventor intended to claim but what he claimed in fact. Each feature of the subject matter must be interpreted objectively.[798] The claims are read giving the words, the

forded by Art. 69 EPC can be seen as important contributions to the jurisprudence of Germany," cited by Lord Hoffman in Kirin-Amgen Inc v. Hoechst Marion Roussel, [2005] R.P.C. 9, No. 74.

791 Kirin-Amgen Inc v. Hoechst Marion Roussel, [2005] R.P.C. 9, No. 8.
792 Kirin-Amgen Inc v. Hoechst Marion Roussel, [2005] R.P.C. 9, No. 7.
793 Kirin-Amgen Inc v. Hoechst Marion Roussel, [2005] R.P.C. 9, No. 53.
794 Kirin-Amgen Inc v. Hoechst Marion Roussel, [2005] R.P.C. 9, No. 53.
795 Kirin-Amgen Inc v. Hoechst Marion Roussel, [2005] R.P.C. 9, No. 54.
796 Kirin-Amgen Inc v. Hoechst Marion Roussel, [2005] R.P.C. 9, No. 55.
797 Kirin-Amgen Inc v. Hoechst Marion Roussel, [2005] R.P.C. 9, No 58.
798 Benkard/Ullmann, Patentgesetz, § 14, No. 75.

meaning, and scope that they normally have in the relevant art.[799] In contrast to American patent law, it is not customary under the European patent law system to rely on the prosecution history for claim interpretation.[800] Facts of the prosecution history can only be used for the determination of scope if reported in the patent specification. The German Federal Supreme Court, for example, interpreted a declaration of the patent applicant that patent protection is not sought for a certain embodiment in light of the principle "venire contra factum proprium".[801] Accordingly, a patentee could not claim the patent to cover such an embodiment in a later trial against an alleged infringer, if the patent was based on such waiver and the infringer had been part of the earlier proceedings.[802] Furthermore, not the time of infringement, but the time of priority, is decisive.[803]

2. Doctrine of equivalents

As in the US, a patent claim can be infringed literally, or under the doctrine of equivalents, directly or indirectly. As claim construction rules, the principles developed for the determination of equivalents rely on the Protocol on the interpretation of Art. 69 EPC. The protocol was amended after the revision of the European Patent Convention in 2000. The newly added Art. 2 states for equivalents that "[f]or the purpose of determining the extent of protection conferred by a European patent, due account shall be taken of any element which is equivalent to an element specified in the claims. "[804] This rule fails to provide a definition of equivalents. Therefore, it permits national courts to interpret the doctrine of equivalents in a flexible and fair way. The word "elements" aims to fit with claim language used for chemical inventions.[805] Patent claims have to be understood not only as the starting point but also as the decisive element.[806] The major goal of a scope extension under the doctrine of equivalents is to combine fair protection for the patentee with a reasonable degree of certainty for third parties. On the one hand, an applicant cannot be required to foresee all potential cases where a competitor may depart from the literal meaning of the

799 BGH, 30 IIC 932 (1999) – Tension Screw (Spannschraube); Meier-Beck, Peter, Aktuelle Fragen der Schutzbereichsbestimmung im deutschen und europäischen Patentrecht, GRUR 2003, 905, 906.
800 Benkard/Scharen, EPÜ, Art. 69, No. 27.
801 BGH, 25 IIC 420, 420 (1994) - Moistening Device I (Weichvorrichtung I).
802 Busse/Keukenschrijver, PatG, § 14, No. 74.
803 Benkard/Scharen, EPÜ, Art. 69, No. 64.
804 Meier-Beck, Peter, The Scope of Patent Protection - The test for Determining Equivalents, 36 IIC 339, 340 (2005); who notes that Art. 69(1) EPC remains unchanged and merely lays down by what means the extent of protection should be determined.
805 Nack, Ralph/Phélip, Bruno, Diplomatic Conference for the Revision of the European Patent Convention, Munich, 20 – 29 November 2000, 32 IIC 200, 207 (2001).
806 See Chapter 4 B II 2.V.

claims.[807] On the other hand, the principle of legal certainty requires that a person using the patent must be able to understand with ease what is protected.[808] The suitable standard for determining equivalents is considered to be the person skilled in the art.[809]

a) Moulded Curbstone

Before 1978, patents were granted under the „Three-Parts-Doctrine“ (Dreiteilungslehre). Under this approach, the patent scope was based on the patentable subject matter.[810] The patentable subject matter was considered the technical teaching included in the patent claims and understood by the skilled person without inventive activity, but in light of the patent description, potential drawings, skilled knowledge and the state of the art.[811]

The newer law is summarized in the case of *Moulded Curbstone*.[812] In this decision, the invention was a moulded curbstone, which assured safe and reliable drainage of rainwater accumulating at the side of a street. The alleged infringer had used conventional stones in the form of cubes or bricks and conventionally rounded curbstones. The German Federal Supreme Court confirmed the doctrine of equivalents, stating that:

> “[t]he question is whether a person skilled in the art … is able to clear up the problem solved by the invention with equally effective means, i. e. to achieve the desired success with other means which also lead to the same result. Solutions, which the average person skilled in the art can determine due to his professional knowledge as being equally effective based on considerations oriented to the invention paraphrased in the claims, will generally fall within the scope of protection of the patent.”[813]

807 BGH, 24 IIC 507 (1993) – Helium Injection (Heliumeinspeisung); Meier-Beck, Peter, The Scope of Patent Protection - The test for Determining Equivalents, 36 IIC 339, 340 (2005).

808 BGH, GRUR 1992, 594, 596 - Mechanische Betätigungsvorrichtung; Reimann, Thomas/Köhler, Martin, Der Schutzbereich europäischer Patente zwischen Angemessenheit und Rechtssicherheit - Anmerkungen zu den Entscheidungen des BGH 'Kunststoffrohrteil', 'Custodiol I', 'Custodiol II', 'Schneidmesser I', 'Schneidmesser II', GRUR 2002, 931, 931; Meier-Beck, Peter, The Latest Issues in German Patent Infringment Proceedings, 32 IIC 505, 511 (2001).

809 Meier-Beck, Peter, The Scope of Patent Protection - The test for Determining Equivalents, 36 IIC 339, 341 (2005). With regard to literal claim construction, the person skilled in the art analyzes and considers the patent claim against the background of his technical knowledge, using description and drawings to assist in claim interpretation.

810 RGZ 2, 325 - Mülltonne; RG GRUR 1940, 543, 545 - Hochglanzphotographien; RG GRUR 1942, 51 - Wischdochte; RG GRUR 1944, 22f - Wellblechofenbekleidung.

811 Lindenmaier, Fritz, Der Schutzumfang des Patentes nach der neueren Rechtssprechung, GRUR 1944, 49, 53; Busse/Keukenschrijver, § 14 No. 13.

812 BGH 18 IIC 795 (1987) – Moulded Curbstone (Formstein).

813 BGH 18 IIC 795, 799 (1987) – Moulded Curbstone (Formstein).

In addition, the court ruled that "the defense that the embodiment attacked and claimed to be an equivalent does not represent a patentable invention in view of the prior art is admissible."[814]Accordingly, the defendant of an infringement process can defend himself, arguing that the claimed embodiment "is known from the prior art, but also by the fact that it is obvious in view of the prior art" ("*Moulded Curbstone* objection").[815] This general understanding of the law comports with the legal framework adopted by most member states of the EPC, although significant differences with respect to the method of determination of scope, or the exact protection granted, remain.[816]

b) Further Decisions

The ruling established in *Moulded Curbstone* was confirmed several times by the German Federal Supreme Court. In its decision *Ione Analysis,*[817] the court stated that the mere approval of an equal effect is not sufficient for equivalents. Rather, the person skilled in the art must be able to predict and determine the means necessary to achieve the equal effect. Accordingly, if the patent claims do not suggest to a person skilled in the art that the described protocol can be modified and still achieve equal effects, equivalents do not exist. This standard, the court emphasized, is required by the principle of legal certainty.[818] The importance of legal certainty has been affirmed in the decision *Handle Cord for Battery* in which the German Federal Supreme Court criticized the decision of the lower court to interpret the claims predominantly on the grounds of the patent description.[819] The claims must entirely describe the essential elements of the invention. Recapitulating, the court ruled that the claims are no longer merely a point of departure but the decisive basis ("massgebliche Grundlage") for determining the extent of protection. As for equivalents, a skilled person should thus be able to determine the equivalent scope on grounds of the claim, his general skills in the art, and simple experimentation.[820]

The German Federal Supreme Court has developed clear guidelines for dealing with equivalents in a number of cases related to the question of whether figures or measurements allow some degree of approximation (and if so, to what degree). Below,[821] a concrete claim analysis under German law will closely examine the deci-

814 BGH 18 IIC 795, 800 (1987) – Moulded Curbstone (Formstein).
815 BGH 18 IIC 795, 800 (1987) – Moulded Curbstone (Formstein); Meier-Beck, Peter, The Scope of Patent Protection - The test for Determining Equivalents, 36 IIC 339, 344 (2005). The author formulates the question of whether the variant, having regard to the state of the art, lacks novelty, or is obvious to a person skilled in the art.
816 Domeij, Bengt, Pharmaceutical Patents in Europe, Stockholm 2000, 314.
817 BGH, 22 IIC 249 (1991) – Ione Analysis (Ionenanalyse).
818 BGH, 22 IIC 249, 255 (1991) – Ione Analysis (Ionenanalyse).
819 BGH, 22 IIC 104 (1991) - Handle Cord for Battery Case (Batteriekastenschnur).
820 BGH, 22 IIC 104, 106 (1991) Handle Cord for Battery Case (Batteriekastenschnur).
821 Chapter 4 c IV 3 b) aa).

sions of *Plastic Pipe,* [822] *Custodiol I*[823], *Custodiol II*[824], *Cutting Blade I*[825] and *Cutting Blade II*[826]. The major principles derived from these cases will then be applied to 3-D protein structure related claims. Also, the principles regarding the cases in which infringement is based on inventive activity will be reviewed and – if necessary – applied to the context of proteomic inventions. In principle, the time for determining infringement is the priority date.[827]

III. Research/Experimental Use Exemption

Finally, this chapter will briefly discuss the limitations of patent protection through the means of experimental use exemption. This is not primarily a question of how the patent scope is determined. Nevertheless, the question of appropriate scope must take into account that a sufficient research exemption enables scientists to use patented knowledge without establishing infringement. This possibility assigns a different weight to the question of what the public can expect from an inventor in exchange for the public protection of his intellectual property rights.

1. Germany

The German Patent System provides an explicit statutory research exemption.[828] According to Section 11 No. 2 GPA, research is explicitly excluded from the patent right.[829] The provision provides that "the rights conferred by a patent shall not extend to acts done for experimental purposes that are related to the subject-matter of the patented invention." The German Federal Supreme Court dealt intensively with

822 BGH, 34 IIC 302 (2003) – Plastic Pipe (Kunstoffrohrteil).
823 BGH, GRUR 2002, 523 – Custodiol I.
824 BGH, 34 IIC 197 (2003) – Custodiol II.
825 BGH, 33 IIC 873 (2002) - Cutting Blade I (Schneidmesser I).
826 BGH, GRUR 2002, 519 – Cutting Blade II (Schneidmesser II).
827 BGH, 33 IIC 525, 535 (2002) – Snow Removal Plate (Räumschild); Kraßer, Rudolf, Patentrecht: ein Lehr- und Handbuch zum deutschen Patent- und Gebrauchsmusterrecht, europäischen und internationalen Patentrecht, 5. Aufl., München 2004, 753; Busse/Keukenschrijver, PatG, § 14, No. 90.
828 Kraßer, Rudolf, Patentrecht: ein Lehr- und Handbuch zum deutschen Patent- und Gebrauchsmusterrecht, europäischen und internationalen Patentrecht, 5. Aufl., München 2004, 812-816; see further Straus, Joseph, On the Admissibility of 'Biological Equivalents Tests' During the Patent Term for Obtaining a Regulatory Approval for Patented Drugs by Third Parties, AIPPI Journal of the Japanes Group November 1998, 211; Herrlinger, Karolina A., Die Patentierung von Krankheitsgenen: dargestellt am Beispiel der Patentierung der Brustkrebsgene BRCA 1 und BRCA 2, München 2005, 234.
829 Straus, Joseph, Abhängigkeit bei Patenten auf genetische Information - ein Sonderfall, GRUR 1998, 314, 318.

the question of research exemption in its *Clinical Trial*s cases.[830] In *Clinical Trial I*, the defendants were conducting clinical studies with the active substance interferon gamma to ascertain further indications.[831] The Federal Supreme Court determined that it was in the public interest that clinical trials for finding further medical uses be excluded from patent infringement, but only if the tests are performed in the course of knowledge acquisition.[832] According to the Court's view, it was irrelevant that the tests also could be used for obtaining regulatory marketing approval:

> "Since the patent act, without further restrictions, exempts from the effect of the patent any act for test purposes that focuses on the subject matter of the invention, it cannot be of any consequence to the admissibility of such tests for what purposes they are being conducted, whether they are intended, possibly, to substantiate an application of pharmaceutical approval, or whether they represent a purely scientific research project."[833]

Based on the above, all testing activities are exempted provided they are performed in the course of knowledge acquisition and are directed to the subject matter of the invention. This includes methods used in order to determine the effects of substances, which were disclosed in previous applications.[834] In *Clinical Trials II*, the defendant conducted clinical trials to confirm results obtained in animal tests and at the same time to gather data necessary for the pharmaceutical approval and marketing of his product.[835] The conducted process resulted in a recombinant, human Erythropoietin ("EPO") called rHu Epo-Merckle. The plaintiff alleged that the amino acid sequence of this "Epo" product corresponded exactly with the amino acid sequence of his patented "Epo", why the patent was infringed.[836] The District Court held that the patent was infringed and the Higher District Court rejected the defendant's appeal. The Higher District Court found that the conducted activities were not directed to further development and improvement of the patented compound, but rather were "undertaken only in order to obtain data for the legal pharmaceutical permission and therefore served commercial interests rather than scientific purpos-

830 See BGH, 28 IIC 103, 103 (1997) - Clinical Trials I (Klinische Versuche I); [1998] R.P.C. 423
Clinical Trials II ; Federal Constitutional Court, 1 BvR 1864/95 of 05/10/2000, paragraphs No. 1 - 38, http://www.bverfg.de/entscheidungen/ rk20000510_1bvr186495en.html, last checked on January 21, 2008. See also Garde, Tanuja, The Effect of Disparate Treatment of the Experimental Use Exemption on the Balancing Act of 35 U.S.C. § 104, 35 IIC 241, 255 (2004).

831 BGH, 28 IIC 103, 103 (1997) - Clinical Trials I (Klinische Versuche I).

832 BGH, 28 IIC 103, 103 (1997) - Clinical Trials I (Klinische Versuche I).

833 BGH, 28 IIC 103, 111 (1997) - Clinical Trials I (Klinische Versuche I).

834 Straus, Joseph, On the Admissibility of "Biological Equivalents Tests" During the Patent Term for Obtaining a Regulatory Approval for Patented Drugs by Third Parties, AIPPI Journal of the Japanese Group November 1998, 211, 225-226.

835 [1998] R.P.C. 423, 423 - Clinical Trials II (Klinische Versuche II), with an early and detailed analysis of the underlying decision of the lower district court, see Straus, Joseph, Zur Zulässigkeit klinischer Untersuchungen am Gegenstand abhängiger Verbesserungserfindungen, GRUR 1993, 308, 311; further Garde, Tanuja, The Effect of Disparate Treatment of the Experimental Use Exemption on the Balancing Act of 35 U.S.C. § 104, 35 IIC 241, 256 (2004).

836 [1998] R.P.C. 423, 427 - Clinical Trials II (Klinische Versuche II).

es."[837] The German Federal Supreme Court held that the defense of experimental use applies to all experimental acts that are directed to the subject matter of the invention. [838] The exemption would be granted "regardless of the purpose for which these results will ultimately be used."[839] Thus, section 11 No. 2 GPA "exempts clinical experiments with a protective agent even in a case where these experiments were exclusively … carried out in order to obtain data" for pharmaceutical approval.[840] Accordingly, the alleged research activities were found to be permissible under Section 11 No. 2 GPA.[841]

In 2000, five years after the *Clinical I* ruling of the Federal Supreme Court, the Federal Constitutional Court addressed the question of whether the exemption for clinical trials to find further indications of the active agent of interferon gamma (used in the drug polyferon) was constitutional.[842] The exclusive licensee of the patent to polypeptides with human interferon gamma properties complained that the lower court's reading of Section 11 No. 2 GPA, to "regard clinical trials which involve a pharmaceutical drug under patent protection as acts of use to which the effects of the patent do not extend", was not compatible with Art. 14(1), sentence 1 GG, which set forth the protection of ownership.[843] The Federal Constitutional Court confirmed the ruling of the lower court, affirming that "unlimited protection of the patent …. is not justified in cases in which this hinders technical development."[844] The Federal Constitutional Court admitted, that the clinical trials at issue could lead to the grant of use patents which otherwise would not have been obtained, but found that this was something the patentee had to tolerate, as he could "only be rewarded for their own contribution to technical advancement."[845] Therefore, the court concluded that the lower court's reading of Section 11 No. 2 GPA did not infringe Art. 14(1), sentence 1 GG.[846]

837 [1998] R.P.C. 423, 423 - Clinical Trials II (Klinische Versuche II). See also Garde, Tanuja, The Effect of Disparate Treatment of the Experimental Use Exemption on the Balancing Act of 35 U.S.C. § 104, 35 IIC 241, 257-258 (2004).

838 [1998] R.P.C. 423, 432-433 - Clinical Trials II (Klinische Versuche II).

839 [1998] R.P.C. 423, 431 - Clinical Trials II (Klinische Versuche II).

840 [1998] R.P.C. 423, 432 - Clinical Trials II (Klinische Versuche II).

841 [1998] R.P.C. 423, 438 - Clinical Trials II (Klinische Versuche II).

842 Federal Constitutional Court, 1 BvR 1864/95 of 05/10/2000, paragraphs No. (1 - 38), available at http://www .bverfg.de/entscheidungen/rk20000510_1bvr186495en.html, last checked on January 21, 2008.

843 Federal Constitutional Court, 1 BvR 1864/95 of 05/10/2000, paragraphs No. 1, available at http://www.bverfg. de /entscheidugen/rk20000510_1bvr186495en.html, last checked on January 21, 2008.

844 Federal Constitutional Court, 1 BvR 1864/95 of 05/10/2000, paragraphs No. 30, available at http://www.bverfg.de/entscheidungen/ k20000510_1bvr186495en.html, last checked on January 21, 2008.

845 Federal Constitutional Court, 1 BvR 1864/95 of 05/10/2000, paragraphs No. 31, available at http://www.bverfg.de/entscheidungen/rk20000510_1bvr186495en.html, last checked on January 21, 2008.

846 Federal Constitutional Court, 1 BvR 1864/95 of 05/10/2000, paragraphs No. 36, available at

It remained questionable whether the research exemption provided by the German courts covers the special case of bioequivalence trials.[847] Bioequivalence trials are carried out to prove for a third party, e.g., the marketing approval institution, that a generic product is bioequivalent, i.e. produces same effects like a patented substance.[848] Based on the above, the general rule laid down in the *Clinical Trial* cases is that the research exemption under German law covers any act conducted for the acquisition of knowledge, notwithstanding the purpose for which this knowledge is eventually used. Hence, the law requires finality with respect to the testing activity and its specific purpose. The testing activity must refer to the patented subject matter and its technical teaching and be performed for gaining knowledge about its decisive properties, effects and uses. Furthermore, studies and research must be undertaken for the advancement of technological progress. Finally, even if all these requirements are met, clinical trials may still not be covered by the research exemption, if they were performed to such an extent that a justification on research grounds is no longer valid. [849]

Bioequivalence trials exclusively focus on showing that a generic drug product has identical properties as the patented product.[850] They serve the main purpose of demonstrating that a generic drug has properties identical to a patented pharmaceutical. The properties, and effects, including side effects of the active patented ingredient, however, have already been analyzed and are generally known at the time the bioequivalent trial is conducted. Typically, bioequivalence is tested early on in order to enter the market as soon as possible after a patent expires. Thus, instead of clarifying properties, effects, possible uses and production feasibility of the patented drug, bioequivalence trials reflect competitive goals, such as an optimized marketing price. Their performance neither intends to ascertain knowledge about the patented subject matter, nor relates to its technical teaching. Under the principles developed in *Clinical Trials I* and *II* and confirmed by the Federal Constitutional court, bioe-

http://www.bverfg.de/entscheidungen/rk20000510_1bvr186495en.html, last checked on January 21, 2008.

847 Straus, Joseph, On the Admissibility of "Biological Equivalents Tests" during the Patent Term for Obtaining a Regulatory Approval for Patented Drugs by Third Parties, AIPPI Journal, November 1998, 211, 229.

848 Straus, Joseph, On the Admissibility of "Biological Equivalents Tests" during the Patent Term for Obtaining a Regulatory Approvla for Patented Drugs by Third Parties, AIPPI Journal, November 1998, 211, 217. As defined in 21 CFR 320.1(e), bioequivalency means "the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study."

849 Straus, Joseph, On the Admissibility of „Biological Equivalents Tests" during the Patent Term for Obtaining a Regulatory Approvla for Patented Drugs by Third Parties, AIPPI Journal, November 1998, 211, 229.

850 Straus, Joseph, On the Admissibility of „Biological Equivalents Tests" during the Patent Term for Obtaining a Regulatory Approval for Patented Drugs by Third Parties, AIPPI Journal, November 1998, 211, 217.

quivalence trials must therefore be considered patent infringement. Any research that obviously does not result in any contribution to the technological progress cannot justify an exemption from a patent.[851]

The question of whether bioequivalent test activities fall under the research exemption must be decided differently under the subsequently adopted Bolar-type exemption.[852] In September 2005, the Bolar-type exemption of the EU Directive 2004/27/EC on the Community Code relating to medicinal products for human use was implemented into the German Patent Law.[853] Section 11 No. 2(b) GPA now exempts all trials and studies that are necessary to obtain marketing approval for the European Union or for one of the Member States. These activities, including trials conducted by generic product manufacturers, are typically not covered by the research exemption, since the experiments have an obvious commercial motivation and are not of a purely scientific nature.[854]

2. U.S.

The U.S. patent system has long provided an experimental use exception.[855] Its jurisprudential origin is *Whittmore vs. Cutter, 1 Gall.*[856], where the court determined that an infringer must have the intention to use a patented invention for commercial profit. The court held that

851 Straus, Joseph, On the Admissibility of „Biological Equivalents Tests“ during the Patent Term for Obtaining a Regulatory Approval for Patented Drugs by Third Parties, AIPPI Journal, November 1998, 211, 230.

852 The term “bolar” is derived from Roche Products, Inc. v. Bolar Pharmaceutical Co., Inc., in which the Federal Circuit reversed the lower court’s decision in Roche, and determinded that “use” under Section 271(a) U.S.C. to cover any “use” of patented subject matter, including using a patented compound to ascertain knowledge for obtaining the approval of a generic version of that compound. See Roche Products, Inc. v. Bolar Pharmaceutical Co., Inc., 733 F.2d 858, 865-66 (Fed. Cir. 1984). As a result, the U.S. Congress adopted Section 271(e)(1); Vihar R. Patel, Are patented research tools still valuable? Use, intent, and a rebuttable presumption: a proposed modification for analyzing the exemption from patent infringement under 35 U.S.C. § 271(e)(1), 47 IDEA 407, 413.

853 Directive 2004/27/EC of the European Parliament and of the Council of 31 March 2004 amending Directive 2001/83/EC on the Community code relating to medicinal products for human use, available at http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:32004L0027:EN:HTML, last checked on January 21, 2008. Art. 10(6) of the Directive reads as: „Conducting the necessary studies and trials with view to the application of paragraphs 1, 2, 3, and 4 [of Art. 10 2004/27/EC] and the consequential practical requirements shall not be regarded as contrary to patent rights or to supplementary protection certificates for medicinal products“.

854 Pfaff, Esther, “Bolar” Exemptions - A Threat to the Research Tool Industry in the U.S. and the EU?, 38 IIC 258, 259 (2007).

855 Herrlinger, Karolina A., Die Patentierung von Krankheitsgenen: dargestellt am Beispiel der Patentierung der Brustkrebsgene BRCA 1 und BRCA 2, München 2005, 262.

856 Whittemore v. Cutter, 1 Gall. 429, 29 F. Cas, 1120, 1121 (C.C.D. Mass. 1813).

> "it could never have been the intention of the legislature to punish a man who constructed such a machine merely for philosophical experiments, or for the purpose of ascertaining the sufficiency of the machine to produce its described effects."[857]

In *Madey v. Duke*[858], the CAFC substantially narrowed the experimental use exception. Madey, a former Professor at Duke University, owned two patents covering equipment in the laboratory of Duke. After a dispute, he left the university. Nevertheless, Duke continued to use some of the patented instruments. Subsequently, Madey sued Duke for, among other things, infringement of the two patents.[859] The Court found that the conducted research is not exempted from patent infringement.[860] Instead, the Court concluded that a "very narrow and strictly limited experimental use defense" is solely available if the use of the invention is "for amusement, to satisfy idle curiosity, or for strictly philosophical inquiry".[861] Furthermore, one can only rely on the defense if the use is "in furtherance of the alleged infringer's legitimate business, regardless of commercial applications" or of its status as profit or non-profit.[862]

With regard to inventions involving biotechnological material, Section 271(e)(1) U.S.C. provides an exception from infringement for activities involving the development and submission of information for U.S. Food and Drug Administration (FDA) approval.[863] The provision states that

> [i]t shall not be an act of infringement to make, use, offer to sell, or sell within the United States or import into the United States a patented invention (other than a new animal drug or veterinary biological product (as those terms are used in the Federal Food, Drug, and Cosmetic Act and the Act of March 4, 1913) which is primarily manufactured using recombinant DNA, recombinant RNA, hybridoma technology, or other processes involving site specific genetic manipulation techniques) solely for uses reasonably related to the development and submission of information under a Federal law which regulates the manufacture, use, or sale of drugs or veterinary biological products.

857 Whittemore v. Cutter, 1 Gall 429, 29 Fed. Cas. 1120, 1121. By "philosophical" experiments Justice Story was referring to "natural philosophy," the term later used for what we today understand as "science", see Integra Lifesciences I, Ltd. v. Merck KgaA, 331 F.3d 860, (C.A.Fed. (Cal.) 2003), 875 (FN8).

858 Madey v. Duke University, 307 F.3d 1351, (Fed. Cir. 2002), cert. denied by Duke University v. Madey, 539 U.S. 958 (2003).

859 Madey v. Duke University, 307 F.3d 1351, 1352-1353; Garde, Tanuja, The Effect of Disparate Treatment of the Experimental Use Exemption on the Balancing Act of 35 U.S.C. § 104, 35 IIC 241, 245-246 (2004).

860 Madey v. Duke University, 307 F.3d 1351, 1362, see also Lentz, Edward T., Pharmaceutical and Biotechnology Research After Integra and Madey, 23 Biotechnology Law Report 2004, 265, 271.

861 Madey v. Duke University, 307 F.3d 1351, 1362.

862 Madey v. Duke University, 307 F.3d 1351, 1362.

863 The rule to permit experimentation with patented inventions by exempting from infringement those activities that are related to seeking regulatory approval from the federal government is also referred to as "clinical research exemption", see Steffe, Eric K./Shea, Tomothy J., JR., Drug Discovery and the Clinical Research Exemption from patent Infringement, 22 Biotechnology Law Report August 2003, 369, 369.

In *Merck and Integra*[864], the US Supreme Court dealt with the question of whether uses of patented inventions in preclinical research, the results of which are not ultimately included in a submission to the Food and Drug Administration (FDA), are exempted from infringement by 35 U. S. C. §271(e)(1).[865] The Federal Circuit Court had clearly confirmed previously the application of this rule, allowing a broader interpretation of experimental use exception "solely for uses reasonably related to the development and submission of information".[866] The Federal Circuit held that Merck's research was not clinical testing to supply information to the FDA, but only biomedial research to identify pharmaceutical compounds, which is why Integra's patents were infringed.[867] The U.S. Supreme Court reasoned that the legislator did not intend Section 271(e)(1) to be so narrowly interpreted and that any infringing activity related to pre-clinical research cannot be classified as infringement::

> "The use of patented compounds in preclinical studies is protected under §271(e)(1) at least as long as there is a reasonable basis to believe that the compound tested could be the subject of an FDA submission and the experiments will produce the types of information relevant to an IND or NDA. The statutory text makes clear that §271(e)(1) provides a wide berth for the use of patented drugs in activities related to the federal regulatory process, including uses reasonably related to the development and submission of any information under the FDCA. "[868]

On remand from the Supreme Court, the CAFC applied the broad interpretation of the research exemption to the Integra case and reversed the district court's judgment of infringement.[869] Applying the principles set forth by the Supreme Court, the CAFC concluded that the allegedly infringing experiments were conducted "for the purposes of determining the optimum candidate angiogenesis inhibitor and proceeding with commercial development of the selected candidate in compliance with regulatory procedures."[870] The Court determined that the FDA research exemption depends on "whether the threshold biological property and physiological effect had already been recognized as to the candidate drug:"[871] Therefore, the fact that Merck's experiments "contributed to scientific knowledge does not deprive them of

864 Merck KGaA v. Integra Lifesciences I, Ltd., 545 U.S. 193 (2005). The earlier Federal Circuit's decision Merck KgaA v. Integra Lifesciences I, 331 F.3d 860 (Fed. Cir. 2003) was vacated and remanded. See also Lentz, Edward T., Pharmaceutical and Biotechnology Research After Integra and Madey, 23 Biotechnology Law Report 2004, 265.

865 The exemption is governed by the Hatch-Waxman Act (1985): It shall not be an act of infringement to make, use, offer to sell, or sell… or import… a patented invention solely for uses reasonably related to the development and submission of information under a federal law which regulates the manufacture, use or sale of drugs… (§ 35 US.C. § 271(e)(1).

866 Merck KGaA v. Integra Lifesciences I, 331 F.3d 860, 868.

867 Merck KgaA v. Integra Lifesciences I, 331 F.3d 860, 866-868.

868 Merck KGaA v. Integra Lifesciences I, Ltd., 545 U.S. 193, 193. The ruling of the Supreme Court direclty applies the reasoning of Eli Lilly & Co. v. Medtronic, Inc., 496 U. S. 661, 665–669.

869 Merck KGaA v. Integra Lifesciences I, Ltd., 496 F.3d 1334 (Fed. Cir. 2007).

870 Merck KGaA v. Integra Lifesciences I, Ltd., 496 F.3d 1334, 1340.

871 Merck KGaA v. Integra Lifesciences I, Ltd., 496 F.3d 1334, 1347.

a safe-harbor benefit of Section 271(e)(1) when the requirement therefore was met."[872]

Although the *Merck* decision did not establish a clear research exception, it clarified the scope of the legislative exception for research in the context of drug and medical device development for regulatory approval. Neither the Supreme Court nor the CAFC examined on remand whether there exists any historical experimental use exemption to infringement. The CAFC avoided the question of how a case based on research-tool patents should be decided, referring to a post-hearing letter in which the parties had stated that those were not at issue.[873] In a dissenting opinion, Judge Rader disagreed with the conclusion that the court had not ruled on the questions of research tools patents, finding that two of these patented processes "have no application outside the laboratory".[874] From his view, the leading opinion "expands the exemption beyond the Supreme Court limits on the provision to eliminate protection for research tool inventions."[875] Under the Supreme Court ruling, the § 271(e)(1) exemption covers research related to information that will ultimately be submitted to the FDA, not "patented processes and tools beyond the scope of the patented compounds" covered by such a research exemption.[876]

In sum, the European patent system provides a much broader opportunity to conduct free research than the U.S. system. The German case, where even activities related to the commercialization of the product are covered, is a good example. Further harmonization of both systems[877], e.g., an adaptation of the European standard in the U.S., may create conditions preventing US scientists from conducting their research abroad where broader research is allowed without causing any risk of patent infringement.[878]

872 Merck KGaA v. Integra Lifesciences I, Ltd., 496 F.3d 1334, 1347.
873 Merck KGaA v. Integra Lifesciences I, Ltd., 496 F.3d 1334, 1348.
874 Merck KGaA v. Integra Lifesciences I, Ltd., 496 F.3d 1334, 1349.
875 Merck KGaA v. Integra Lifesciences I, Ltd., 496 F.3d 1334, 1348.
876 Merck KGaA v. Integra Lifesciences I, Ltd., 496 F.3d 1334, 1348.
877 The different approaches of the European and U.S. patent law system are also caused by different university cultures. In Europe, universities usually are public institutions, whereas universities in the U.S. are often organized in a similar fashion to private companies. In spite of being a public institution, the University of California, for example, is the leading patent holder in the biotech sector, Malakoff, David, Intellectual property. NIH roils academe with advice on licensing DNA patents, 303 Science 2004, 1757, 1757.
878 The decision of Bayer v. Housey stongly emphasiszed the incentive of scientists to conduct research abroad. Garde, Tanuja, The Effect of Disparate Treatment of the Experimental Use Exemption on the Balancing Act of 35 U.S.C. § 104, 35 IIC 241, 259 (2004). Nevertheless, the Human Genome Organization ('HUGO') recommends that the European model of experimental use exception is used as a universal template, see Straus, Joseph, HUGO Statement on the Scope of Gene Patents, Research Exemption, and Licensing of Patented Gene Sequences for Diagnostics, 2003, 2.

C. Use of 3-D protein structure (concrete claim analysis)

As mentioned earlier, the first patents on gene sequences did raise concerns regarding their potentially undue scope of protection.[879] Did these critical voices prove to be correct? To answer this question, it is important to ask whether claims on later disclosed structural properties depend on previously granted gene patents or other intellectual property rights. Patent dependency refers to a situation in which a new invention cannot be used without the infringement of an earlier one. It applies, although the scope of protection of the earlier patent does not include the technical teaching of the later one as such. The German case law did solve this situation of conflict by determining that the use of a dependent patent without the approval of the earlier patentee is not allowed.[880] However, the holder of the earlier patent is not allowed to use the later invention without the approval of this patentee. Thus, the right of the earlier patentee to prohibit the use of the later patent does not result in a right to actually use the later-issued patent.[881] Patent dependency, however, is only established if the later-developed invention can be carried out without any further inventive activity of the person skilled in the art. In *Segmentation Device for Trees*, the plaintiff owned the German patent No. 29 18 622 (the "contract patent") for the process for segmenting logs into wood products. The defendant was the proprietor of German patent No. 35 14 892 (the '892 patent') to a "process and device for chipping wood, in particular for segmenting logs with wanes by chipping."[882] The parties concluded a license agreement. Thereby, the plaintiff granted the defendant a license for the "contract patent" in exchange for a certain license fee. The German Federal Supreme Court had to decide whether the license agreement covered the use of defendant's '892 patent. The lower court held that the patented invention of the defendant was a further development of the contract patent that fine-tuned and adjusted its technology. More specifically, it had to be seen as an equivalent of the contract patent, which a person skilled in the art would be able to predict and carry out. Therefore, the invention of the defendant was considered an equivalent means, which depended on the contract patent and was covered by its scope of protection.[883] The German Federal Supreme Court found that the additional cutting blade used within the patented process of the patentee could only be considered an equivalent device to the technology covered by the process patent if it did not involve any in-

879 Chapter 3 A II 2 a); see also Straus, Joseph, Abhängigkeit bei Patenten auf genetische Information - ein Sonderfall, GRUR 1998, 314; further Pietzcker, Rolf, Die sogenannte Abhängigkeit im Patentrecht, GRUR 1993, 272.

880 Busse/Keukenschrijver, PatG, § 9, No. 39.

881 Straus, Joseph, Abhängigkeit bei Patenten auf genetische Information - ein Sonderfall, GRUR 1998, 314, 316; siehe auch: Krieger, Ulrich, Abhängige Patente und ihre Verwertung (Frage 97), GRURInt. 1989, 216, 216.

882 BGH, 26 IIC 261, 262 (1995) - Segmentation Device for Trees (Zerlegevorrichtung für Baumstämme).

883 BGH, 26 IIC 261, 266 (1995) - Segmentation Device for Trees (Zerlegevorrichtung für Baumstämme).

ventive activity.[884] Based on this reasoning, the court remanded the case to the lower court with the direction to reconsider whether the invention of the defendant required any inventive efforts by a person skilled in the art. In such a case, the court determined, patent dependency under the principle of the doctrine of equivalents would not be established.[885]

The answer as to whether patent dependency in the case of 3-D protein structure claims exists will be provided by means of a concrete claim analysis. This will be accomplished from the perspective of an absolute compound protection, the most applied principle in Europe and the U.S. In Europe, the European Directive 98/44/EC was interpreted on behalf of an absolute scope.[886] In Germany, absolute compound protection is the leading principle except for the patenting of human genome sequences, for which § 1a GPA incorporates the principle of purpose-related compound protection.[887] In the U.S., the patent scope is discussed in the context of claim construction.[888] Broad claims are allowed if sufficiently supported by a written description.[889]

First, it will be attempted to determine whether the use of 3-D structures obtained from natural sources and from crystalline proteins violates patents related to a recombinant protein. A major focus will then be the question of infringement through the use of sequence-dissimilar proteins sharing common folds. This issue resembles the problem with protein variants and demonstrates why the legal principles existing in this area are of particular interest. The next step will focus on the relationships between selection inventions and inventions involving the entire molecule. Further, the use of identified compounds is examined with respect to an infringement of the underlying patented screening method. Finally, some remarks will be made with regard to the infringement of 3-D protein analysis techniques. Claim constructing rules of both Europe and the U.S. will play a particular role in the application of the doctrine of equivalents.

884 BGH, 26 IIC 261, 267 (1995) - Segmentation Device for Trees (Zerlegevorrichtung für Baumstämme).

885 BGH, 26 IIC 261, 269 (1995) - Segmentation Device for Trees (Zerlegevorrichtung für Baumstämme).

886 Benkard/Scharen, EPÜ, Art. 69, No. 45. The before applied principle of absolute compound protection was not changed with the implemenation of the directive. See also Feldges, Joachim, Ende des absoluten Stoffschutzes? Zur Umsetzung der Biotechnologie-Richtlinie, GRUR (2005) 977, 981.

887 § 1a (4) GPA states: "If the subject matter of the invention is a sequence or partial sequence of a gene the structure of which is identical to the structure of a natural sequence or partial sequence of a human gene, its use, the susceptibility of industrial application of which is concretely described … is to be included into the claim."

888 Phillips v. AWH Corp., 415F.3d 1303, 1313 (Fed. Cir. 2005) (en banc).

889 As for the dispute surrounding the requirement of such "separate written description", see Chapter 2 A III 1c) bb).

I. Use of 3-D structure from naturally obtained proteins

A first question that has to be addressed is whether the use of a 3-D structure from naturally obtained proteins automatically infringes the patent covering the recombinant produced protein. As an example, consider patents that are directed towards methods for preparing "erythropoietin products" from urine or other human sources.[890] In recent years, a number of inventions from this group reached patent offices. A representative claim to such a product can be expressed as follows:[891]

> A method for the preparation of an erythropoietin product having no inhibitory effect against erythropoiesis which comprises the steps of
>
> (a) adsorbing a crude erythropoietin product obtained from the urine of healthy human onto a weakly basic anion exchanger from a neutral or weakly acidic aqueous solution in the presence of an inorganic neutral salt in a concentration in the range from 0.1 to 0.2 mole per liter, and
>
> (b) eluting the thus adsorbed erythropoietin product with an aqueous eluant solution containing an inorganic neutral salt in a concentration in the range from 0.5 to 0.7 mole per liter. [892]

In view of such a claim and its relation to a patented recombinant protein, it is at least possible that anyone who uses the patented proteins may be an infringer and consequently may be liable for damages. According to patent law standards, infringement exists if a patented product or process is used. To establish infringement of the recombinant protein's patent, it is therefore reasonable to require that the genetic information must be used. Obtaining a protein from natural sources, however, does not require the use of any recombinant methods. The protein is isolated as such and is independently obtained from the genetic encoding process.[893] Consequently, no infringement exists. Claims directed to natural purified proteins must be con-

890 U.S. patent, No. 3,033,753, discloses a method for isolating erythropoietin from sheep blood plasma. Low yields of a crude solid extract containing erythropoietin are provided. Further isolation techniques encompass immunological procedures. Antibodies directed to erythropoietin are produced by injecting an animal, such as a rat or a rabbit, with human erythropoietin. The immune system of the animal recognizes the injected substance as a foreign antigenic compound and stimulates the production of antibodies against the antigen. When the blood is extracted, the antigenic activity remains in the serum. The unpurified serum may then be used in assays to detect and complex with human erythropoietin. The resulting proteins, however, encompass various disadvantages. The serum antibody is 'polyclonal' in nature and will combine with substances other than erythropoietin. (See description of U.S. patent No. 5, 547,933 (August 20, 1996)). Even if other polyclonal and monoclonal antibodies used by different methods may provide highly useful material for the detection of erythropoietin, it appears unlikely that they can provide sufficient quantities.

891 Note that below we consider an invention that entails the use of erythropoietin's structural properties in the context of compounds identified through 3-D screening methods.

892 U.S. Patent No. 4,397,840 "Novel erythropoietin product and method for the preparation thereof" to Takezawa, et al, Tokyo 1983.

893 U.S. Patent No. 4,397,840 "Novel erythropoietin product and method for the preparation thereof" to Takezawa, et al, Tokyo 1983.

strued as being limited to the amino acid as such. Patent dependency is not established.

This result holds both for Europe and the U.S., with a similar line of reasoning. Although natural proteins contain the information from the underlying genetic code, they do not belong to the patent directed to the gene sequence. The naturally occurring protein is therefore not included in the patent coverage of gene patents. To understand this result, one can also refer to the distinction between discovery and invention. Non-isolated, naturally occurring gene sequences are considered discoveries.[894] Thus, proteins that are encoded by naturally occurring gene sequences are also discoveries. The isolation of a gene is the basic requirement for establishing the gene's patentability.[895] The non-isolated gene in its natural environment (e.g. the human body) cannot be viewed as novel. Consequently, a naturally occurring protein that was encoded by a naturally occurring gene sequence is not covered by patents directed to isolated genes. Further, it fails to create novelty, unless it is separated and purified from its natural surroundings.[896]

From this perspective, it would seem to be cost-effective to make extensive use of naturally obtained proteins, because licensing expenditures would not accrue. However, attempts to obtain proteins from natural sources have proven relatively unsuccessful. For example, large amounts of erythropoietin are necessary for research purposes, clinical testing, and pharmaceutical applications. The last include medical treatments of kidney diseases or other disorders in which the human organism fails to sustain production of erythropoietin. The prospects for recombinant procedures are therefore much better, in terms of a full characterization of mammalian erythropoietin as well as of the provision of high amounts for diagnostic and clinical use.[897] Generally, the amounts produced in nature are too small and not sufficient to design a new drug. Complicated and sophisticated laboratory techniques must be used and generally result in high impurity or unstable pharmaceutical end products.[898] Moreo-

894 Krefft, Alexander Richard, Patente auf human-genomische Erfindungen: Rechtslage in Deutschland, Europa und den USA, München 2003, 267. Thus, the U.S. patent law requires that a claim referring to a gene sequence must always contain the term "isolated", e.g. "isolated polynucleotide".

895 Krefft, Alexander Richard, Patente auf human-genomische Erfindungen: Rechtslage in Deutschland, Europa und den USA, München 2003, 89.

896 Herdegen, Matthias, Patents on Parts of the Human Body: Salient Issues under EC and WTO Law, 5 The Journal of World Intellectual Property 2002, 145ff. The rights conferred by a patent do not extend to the human body and its elements in their natural environment. Patent protection does not include natural substances themselves.

897 As for the prospects of recombinant procedures, see Straus, Joseph, Zur Zulässigkeit klinischer Untersuchungen am Gegenstand abhängiger Verbesserungserfindungen, GRUR 1993, 308, 309.

898 Problem discussed in Amgen Inc. v. Hoechst Marion Roussel, Inc., 314 F.3d 1313 (Fed. Cir. 2003).

ver, various attempts to isolate erythropoietin from urine resulted in unstable and biologically inactive preparations of the hormones.[899]

II. Use of 3-D structure from recombinant proteins

Recombinant techniques are presently more successful for the production of therapeutically effective amounts of proteins.[900] In this context, the first question that emerges is whether the use of the recombinantly produced protein 3-D structures infringes the patent involving the gene sequence. This query is easily solved if the sequence identical protein is used. The patent to the gene sequence that encodes for such a protein is literally infringed under Section § 271(a) U.S.C./Section 139 (1) GPA. It is irrelevant as to whether the protein is used specifically with regard to its 3-D structure. Although the claim to the gene sequence and the encoded protein does not include the structural coordinates as claimed, the structural coordinates are an inherent property of the claimed protein in a particular state. As illustrated in Part II, proteins automatically fold into their final folding stage after they are encoded by the underlying nucleotides.[901] The folding process is initiated as soon as the RNA translates the genetic information. Hence, the use of these proteins includes the tertiary or quaternary structure of the protein and not merely the amino acid sequence in its primary folding stage. Recombinant processes encode the protein as a whole, e.g., in its entire tertiary structure. Thus, a patent to the recombinantly produced tertiary structure automatically covers the recombinantly produced primary structure, the amino acid sequence. Accordingly, any patent to the recombinantly produced 3-D protein structure automatically depends on the earlier issued patent to the recombinantly produced amino acid sequences. In other words, in using the subject matter of the 3-D structure patent, the patentee will need to infringe the exclusive rights belonging to the patentee of the amino acids sequences.[902] This reasoning further complies with Art. 9 of Directive 98/44/EC stating that the scope of biotechnological inventions extends to "all material in which the product [consisting of genetic information] is incorporated". The term "incorporated" must be interpreted as referring to genetic information that "is inserted by means of a technical process".[903] A recombi-

899 As stated in U.S. Patent 5,441,868 "Production of recombinant erythropoietin" to Linn, F.K (Thousands Oaks 1995): "Prior attempts to obtain erythropoietin in good yield from plasma or urine have proven relatively unsuccessful. Complicated and sophisticated laboratory techniques are necessary and generally result in the collection of very small amounts of impure and unstable extracts containing erythropoietin."

900 See, for example, U.S. Patent 5,441,868 "Production of recombinant erythropoietin" to Linn, F.K (Thousands Oaks 1995).

901 Chapter B II.

902 Unless the experimental use exception applies.

903 Krefft, Alexander Richard, Patente auf human-genomische Erfindungen: Rechtslage in Deutschland, Europa und den USA, München 2003, 267.

nant protein contains genetic information that was inserted by a recombinant technology.

Legal questions arise if known recombinant technologies are improved or modified in order to enable proteomic research.[904] With recombinant technologies frequently involving problems in 3-D protein structure determination, this issue typically occurs in the field of proteomic research tools. Most proteomic studies must recognize that the proteome changes constantly. Modifications and interactions, binding activity, and self-regulatory adjustments all ensure that the proteome sensitively reacts to the environment. In this context, European patent No. 0636183 "Compositions and Methods For Protein Structural Determinations" is of particular interest.[905] It focuses on the improvement of a recombinant method in order to enable NMR spectroscopy, which otherwise had not been possible. More specifically, the patent involves a new composition and method for the determination of 3-D structures of proteins expressed in cultures of mammalians or insects cells by NMR spectroscopy.[906] It takes into account that most mammalian proteins contain significant post-translational modifications that cannot be effected in bacterial or yeast systems. Existing studies on mammalian and insect cell produced proteins have also been unsatisfactory. Therefore, the patented invention provides a novel method for creating a mammalian or insect cell culture which is capable of producing the protein of interest in a nutrient medium containing all amino acids that are essential for the growth of the cell - in a configuration that permits NMR spectroscopy. The patent is specifically directed to proteins that cannot be analyzed by x-ray crystallography, such as mammalian cell proteins.[907] Claim 1 of European Patent No. 0636183 to "Compositions and Methods For Protein Structural Determinations" reads as follows:

> „A method for determining three-dimensional structural information of a protein, which comprises the steps of (a) growing, under protein-producing conditions, a mammalian or insect cell culture which is capable of producing the protein of interest in a nutrient medium which contains all amino acids that are essential for growth of the cells and which contains assimilable sources of carbohydrate, essential minerals and growth factors, wherein the amino acids and any other substrate used by the cells for protein synthesis in such nutrient medium are substantially isotopically labeled; (b) isolating the labeled form and (c) subjecting the protein to NMR spectroscopic analysis to determine information about its three-dimensional structure. [908]„

The question must be asked of whether the use of the above invention infringes patents involving similar recombinant technologies for the production of the same amino acid sequences. On the one hand, different recombinant technologies produc-

904 Straus, Joseph, Zur Zulässigkeit klinischer Untersuchungen am Gegenstand abhängiger Verbesserungserfindungen, GRUR 1993, 308, 310.

905 European Patent No. 0636183 "Compositions and Methods for Protein Structural Determinations" by Brown, Jonathan M., Columbia 1994.

906 Id.

907 Id.

908 European Patent No. 636183 "Compositions and Methods for Protein Structural Determinations, by Brown, Jonathan M., Columbia 1994.

ing the same amino acid sequences typically use the same gene sequences, which is why infringement should be constituted. On the other hand, Claim 1 is directed to a recombinant technology that for the first time provides a sufficient basis for any conduct of NMR spectroscopy. The question thus is whether it follows that infringement is not established. The new NMR approach, however, still relies on already patented recombinant technology. In conclusion, the method claimed in Claim 1 must be considered an improvement of earlier invented and patented mammalian expression systems. Consequently, Claim 1 depends on any earlier issued patents directed to recombinant technologies being used in the new NMR-related approach and infringement of those patents is constituted.[909]

III. Use of 3-D structure from crystallized proteins

An alternative to obtaining protein 3-D structures from natural or recombinant sources is to crystallize them.[910] Protein crystals are not only used for the determination of structural properties, but have a number of other applications. Lately, studies have shown that they are useful as a means of achieving controlled drug administration. With most drugs being rapidly cleared by the organism following medication, stabilizing a desired drug level in the organism is considered a major challenge. Protein crystals provide significant benefits in the controlled delivery of protein drugs such as insulin or interferon. To ascertain the prescription of correct dosages, uniform sizes must be produced.[911]

A patent on protein crystals can be directed either to the crystallization of the protein *via* a particular procedure, or to the obtained crystals themselves. To establish a comprehensive understanding of related claims, it is useful to consider a number of examples, both from the U.S. and Europe. A second step then focuses on the question of infringement. The following illustrates a U.S. patent claim to the crystals themselves:

> A crystal of a protein-ligand complex comprising a protein-ligand complex of an N-terminal truncated IF4E and a ligand, wherein the crystal effectively diffracts X-rays for the determination of the atomic coordinates of the protein-ligand complex a resolution of greater 5.0 Angstroms; wherein …"[912]

909 The development of the new method might, however, be covered by the research exemption, as for the German case (§ 11 No. 2 GPA), see Straus, Joseph, Zur Zulässigkeit klinischer Untersuchungen am Gegenstand abhängiger Verbesserungserfindungen, GRUR 1993, 308, 310.

910 Chapter 2 E II 2 a).

911 Basu, Sujit K./Govardhan, Chandrika P./Jung, Chu W./Margolin, Alexey L., Protein crystals for the delivery of biopharmaceuticals, 4 Expert Opinion on Biological Therapy 2004, 301, 301.

912 US Patent No. 5,872,011"Crystal of protein-ligand complex containing an N-terminal truncated eIF4E, and methods of use thereof", by Burley, Stephan K./Nahum, Sonnenberg/Marcotrigiano, Joseph/Gingras, Anne-Claude, New York 1999.

The claim has been filed by Rockefeller University, which obtained U.S. patent No. 5,872,011 entitled "Crystal of a protein-ligand complex containing an N-terminal truncated eIF4E, and methods of use thereof."[913] The invention involves a form of the messenger RNA 5' cap-binding protein that can be crystallized with a ligand to form a crystal with sufficient quality to allow detailed crystallographic data to be obtained. Furthermore, the invention comprises the crystals and the three-dimensional structural information, and includes procedures for related structural based drug design using the obtained crystallographic data. As a preferred method, sitting-drop vapor diffusion is utilized to grow the crystal.

By comparison, a claim directed to the crystallization of the protein via a particular procedure can be expressed as in the following claim of US Patent No. 5,872,011:

> A method for determining the three-dimensional structure of a co-complex of [the specified protein] ... which comprises (a) x-ray diffraction data for crystals of the co-complex, and (b) utilizing a set of atomic coordinates selected from the group consisting of [the protein]; a portion thereof; and coordinates having a room mean square deviation therefrom with respect to conserved protein backbone atoms of not more than 0.65 ANG to define the three-dimensional structure of the co-complex. [914]

The claim is directed to the design of an immunosuppressive agent for the treatment of patients suffering from autoimmune disorders and for recipients of transplanted organs. Research efforts have led to the identification of a protein, tyrosine kinase, as a crucial element for immune responses. It was found that blocking the biological function of ZAP-70 leads to immunosuppression. The invention therefore proposes the design of a 3-D structure-based inhibitor of the ZAP-70 protein. It includes the cloning, expression and purification of the ZAP-70, its crystallization, the determination of its tertiary structure and the design of the suitable inhibitor. Using recombinant techniques, the patent depends on any existing patents with regard to such techniques.[915]

913 US Patent No. 5,872,011 "Crystal of protein-ligand complex containing an N-terminal truncated eIF4E, and methods of use thereof", by Burley, Stephan K./Nahum, Sonnenberg/Marcotrigiano, Joseph/Gingras, Anne-Claude, New York 1999.

914 US Patent 5,872,011 "Three dimensional structure of a ZAP tyrosine protein kinase fragment and modeling methods" by Hatada, Marcos H./Lu, Xiaode/Laird, Ellen R./Karas, Jennifer L./Zoller, Mark J./Holt, Dennis A., Cambridge, MA 2001. The term ZAP-70 refers to 'Zeta-chain-associated protein kinase 70'. It is a member of the protein tyrosine kinase family and is normally expressed in T cells and natural killer cells. It plays a critical role in the initiation of T-cell signaling. ZAP-70 is expressed in T cells and tumors of T-cell lineage. A high level of ZAP-70 expression appears restricted to a subgroup of chronic lymphocytic leukemia (CLL). The ZAP-70 gene is in chromosome 2q12, see: http://www.medterms.com /script/main/art.asp?Art.key=23234, last checked on January 21, 2008. Protein kinases are targets for treatment of several diseases. For a description, see Noble, Martin E. M./Endicott, Jane A./Johnson, Louise N., Protein kinase inhibitors: insights into drug design from structure, 303 Science 2004, 1800-1805.

915 Id.

Besides these two characteristic claims, it is useful to consider two further examples of patents granted by the EPO, to show the potential variations inherent in claims directed to crystallization. First, the European patent EP1518925 issued in 2005 covers an invention involving a novel crystal of a glucokinase protein and a drug design method using the 3-D structure coordinates obtained using this crystal. The glucokinase protein is crystallized and its 3-D structure thereof analyzed. In a second step, a binding compound for glucokinase is designed on the basis of the coordinate for the resulting three-dimensional structure.[916] Second, European Patent EP1212365, issued in 2002, covers the crystal structures of domains of the receptor protein tyrosine kinase (RPTK) and their ligands. Determination and use of the RPTK and their ligands are included. Further, the patent discloses the following information: one amino acid group of the receptor includes a 3-D structure of an extracellular domain of RPTKs. The 3-D structure of RPTKs can facilitate the design and identification of modulators of RPTK function. Other such structures can include RPTK ligands, such as stem cell factor or a fragment thereof. Modulators of RPTK function can be used to treat disease mediated by inappropriate RPTK activity.[917]

Having reviewed several representative claims, one has to ask whether the use of 3-D protein structure obtained from a protein crystal infringes the patent to the recombinantly produced amino acid sequence. At first glance, it seems that a protein-crystal-invention does not involve any information which could establish dependency from an underlying gene patent. The process of crystallization as such does not make any use of gene-related information necessary. Protein crystals are obtained from saturated protein solutions.[918] Their production is only possible if sufficient purified proteins are available. Accurate crystallization requires a method capable of producing large amounts of proteins with correct functional characteristics. So far, attempts to obtain proteins from natural sources have proven relatively unsuccessful, which is why most inventions related to drug design or pharmaceutical products prefer the use of recombinant proteins. Recombinant technologies provide the necessary amount and the purification state required for stable end products. Thus, most inventions, such as the one discussed above for the ZAP-70 protein, tend to the use of recombinant proteins.[919]

916 European Patent No. 1518925 "Crystal of Glucokinase Proteins, and method for drug design using the crystal" by Kamata, Kenji/Nagata, Yasufumi/Toshiharu, Iwana, Tokyo 2003.

917 European Patent No. 1212365 "Crystal Structures of Domains of Receptor Protein Tyrosine Kinase and Their Ligands" by Schlessinger, Joseph/Hubbard Stevan/Mohammadi, Moosa/Plotnikov, Alexander/Zhang, Zhongtao/Kong, Xiang-Peng, New York 2002.

918 The term protein solution refers to proteins in aqueous form, see Whitford, David, Proteins: Structure and Function, Chichester, West Sussex, U.K., 358.

919 US Patent No. 5,872,011 "Three dimensional structure of a ZAP tyrosine protein kinase fragment and modeling methods" by Hatada, Marcos H./Lu, Xiaode/Laird, Ellen R./Karas, Jennifer L./Zoller, Mark J./Holt, Dennis A., Cambridge, MA 2001. The patent specification determines a 'naturally occurring' gene encoding the protein being used in the invention.

As for infringement, both patent law systems, i.e. 35 U.S.C. Section 271(a) and § 139(a) GPA require, among others, that a product "is used." Hence, the patent to the 3D crystal may be infringed under the following circumstances. First, anyone who uses the crystallographic data may be liable for damages. Second, anyone who reconstructs and uses the coordinates of the structural features, even with some deliberate errors, may be liable for damages, provided that the existing errors are not essential.[920] The patent to the recombinant production of a certain protein is infringed if the process of obtaining a protein crystal includes the use of patented recombinant processes for the production of such protein. If crystals are obtained without any involvement of patented recombinant techniques, no infringement is constituted. These rules are applicable to both, 35 U.S.C. Section 271(a) and § 139(a) GPA.

From a licensee perspective, the use of protein crystals also appears to be cost-effective. Nevertheless, existing difficulties with crystallization techniques have resulted in the issuance of a relatively small number of patents related to crystalline forms.[921] With crystallizing techniques constantly improving, this might change in the near future. Large firms are addressing the challenge of optimizing protein crystallization. With high quality crystals being largely dependent on a suitable environment, a main focus is the optimization of crystallization conditions.[922] Experience shows that crystallization in a microgravity environment produces crystals having improved properties over crystals prepared under the normal gravity on earth.[923] Hence, scientists use the International Space Station, which provides access to such an environment, for conducting intensive experimental projects. Meanwhile, national agencies, such as the National Aeronautics and Space Administration (NASA)[924] have become leading federal institutions in promoting and funding protein crystallization research. Improved crystallization conditions will help to optimize the properties of obtained crystals, resulting in more accurate 3-D protein structures and advances in drug design.

IV. Use of new proteomics technologies: An example using sequence-dissimilar proteins sharing common 3-D fold

The issue of whether patent claims should be interpreted broadly enough to encompass later-arising technologies that were unknown at the priority date has

920 Barton, John H., United States Law of Genomic and Post-Genomic Patens, 33 IIC 779, 788 (2002).

921 See USPTO and EPO databases. As stated in Burley, Stephan K./Nahum, Sonnenberg/Marcotrigiano, Joseph/Gingras, Anne-Claude, Crystal of protein-ligand complex containing an N-terminal truncated eIF4E, and methods of use thereof, New York, NY 1999, Only few protein crystals have been produced with sufficient quality.

922 See Chapter 2 E II 2 a.

923 http://liftoff.msfc.nasa.gov/shuttle/msl/science/pcg.html, last checked on January 21, 2008.

924 http://www.nasa.gov/, last checked on January 21, 2008. .

been the frequent subject of discussions.[925] The topic is of major importance in the field of proteomics. With the number of disclosed 3-D protein structures constantly increasing, novel proteins might be revealed having the same functions as earlier patented proteins. These later-identified proteins can be considered new technologies for accomplishing known effects. As mentioned above, there exist a number of proteins with essentially no sequence homology that fold into the same tertiary structure.[926]

Proteins involving different amino acid sequences thus may still fold into the same structure and therefore – with the function depending on the structure rather than on the amino acid sequence – provide same effects.[927] Even substantial variations between amino acid sequences may not create any difference within the 3-D conformation or function of the protein.[928] The question thus is whether the use of this protein infringes the patent on a structurally related protein that does not bear the same amino acid sequence, but has the same functions, because of its identical 3-D conformation. Similar issues already arose in the context of protein engineering decades ago. Here, the question was whether the use of protein variants infringes the patent directed to the originally patented protein. This inquiry is a key element in the field of protein science. Unless protein claims cover engineered variants, it can be relatively simple for a competitor to 'design around' a claim merely by generating and commercializing one of these variants.[929] In order to provide deeper insight into the problem, the following section will first briefly illustrate the term of "protein engineering". As a next step, the question of whether the legal categories developed for protein variants are also suitable for proteins performing the same function due to the same 3-D structure will be discussed.

925 T292/85 Polypeptide-Expression/Genentech, OJ 1989, 275, 283; BGH, 33 IIC 525 (2002) – Snow Removal Blade (Räumschild); GRUR 1972, 704, 705 – Wasser-Aufbereitung; GRUR 1975, 593, 596 – Mischmaschine. For the American debate, see Sarnoff, Joshua, The Doctrine of Equivalents and Claiming the Future after Festo, 14 The Federal Circuit Bar Journal 2004, 403, as for the European debate see Falck, Kurt von, Zur Äquivalenzprüfung bei im Prioritätszeitpunk noch unbekannten Ersatzmitteln, GRUR 2001, 905.

926 Chapter 2 B III.

927 Masuoka, Kunihisa, Study on the Ways of Protection of Post-Genome Research Products, IIP Bulletin 2002, 84-95, 88.

928 Holman, Christopher M., Protein similarity score: a simplified version of the blast score as a superior alternative to percent identity for claimng genuses of related protein sequences, 21 Santa Clara Computer & High Tech. L.J. 2004, 55, 58.

929 Holman, Christopher M., Protein similarity score: a simplified version of the blast score as a superior alternative to percent identity for claimng genuses of related protein sequences, 21 Santa Clara Computer & High Tech. L.J. 2004, 55-98, 60.

1. Protein engineering and legal standards for the use of protein variants

The term "protein engineering" encompasses various activities that aim to create novel, non-natively occurring protein structures.[930] Such creation may be achieved by modifying existing polypeptide chains by combining segments or regions of different proteins, or by creating polypeptide sequences *de novo*. The most common form of protein engineering encompasses efforts to illustrate and quantify the fundamental interaction between structure and function, usually in the context of measurement of changes resulting from specific alterations of sequences, as well as studies of homologous amino acids from engineering. Another form, believed to be the "true" protein engineering method, consists of "those experiments in which a protein of improved features is confidently synthesized from a design based on well-understood structure-function relationships". Advances in recombinant DNA techniques during the 1980s enabled scientists to substantially improve the interactive process of modification and measurement.[931] Through measurement in a very short time frame, protein engineers gained the ability to elucidate the dynamics of structure-function relationships between primary sequence data and conformational alteration.[932] Biologists' aim is to develop modified proteins with properties superior to those existing in nature. The process involves altering the nucleotide sequence of the gene such that it encodes a protein with a different amino acid sequence, which in turn alters the protein 3-D structure and function. These "second generation" proteins provide various prospects for inventions. For the average protein, a large amount of unique variants can be created, each differing from the natural sequence by only a single amino acid. In most instances, the modified analogues are functionally indistinguishable from the original protein, and the remaining residues are largely biologically inactive or unpredictable for clinical use due to immunogenic side effects. However, some cases may be pharmaceutically attractive. Because they are unpredictable at the level of amino acid sequence, the disclosure of the polypeptide chain does not automatically enable an ordinary skilled person to make potential pharmaceutical improvements.[933]

An increasing number of new drugs could only be created with the help of modified proteins. The first approved pharmaceutical drug on the market based on pro-

930 Robertson, Dan/Noel, Joseph P., Protein Engineering, San Diego, CA 2004. The book provides a detailed introduction of the methodology of protein engineering and further demonstrates different techniques, including computational and laboratory methods.

931 Basic knowledge of protein engineering also provided in: Sephton, Gregory B., Biotechnology: the doctrine of equivalents and infringement of patented proteins, 25 Suffolk University Law Review 1991, 1035, 1069.

932 Kushan, Jeffrey, Protein Patents and the Doctrine of Equivalents: Limits on the Expansion of Patent Rights, 6 Berkeley Technology Law Journal 1991, 108, 121f.

933 Ryan, L. Antony/Brooks, Roger G., Innovation vs. Evasion: Clarifying Patent Rights in Second-Generation Genes and Proteins, 17 Berkeley Tech. L.J. 2002, 1265, 1280.

tein engineering was Betaseron[934], a bacterially produced alteration of beta interferon that differs from the originally occurring protein by only a single amino acid. Other approved drugs based on protein engineering are Eli Lilly's Humalog (an analog of human insulin), Genentech's TNK case (an alternated form of human tissue plasminogen activator) and Amgens's Infergen[935] (an analog of human alpha interferon).[936]

Bearing great prospects on the one hand, the technique of protein engineering may also elevate risks. It raises *de novo* the problem of patent dependency for protein and gene inventions. From first sight, dominant patents on unmodified genes or proteins should not block those innovative pharmaceuticals. On the other hand, scientists are now able to develop proteins that have the same function as the patented analogues in their competitors' products.[937] This could result in rendering existing patents almost worthless. Thus, the question of whether patents on recombinant genes and proteins cover second-generation analogs is essential.

Protein variants must be distinguished from the analyzed subject matters of sequence-dissimilar proteins sharing common folds. The former typically share a high percentage of sequence similarity[938], whereas the latter often do not have any detectable sequence similarity.[939] Nevertheless, the legal standards developed for infringement by the use of protein variants must also apply *a fortiori* to sequence-dissimilar proteins performing the patented function. Sequence-dissimilar proteins do not bear any sequence similarity but rather share common folds due to their 3-D structure. If the courts apply the strict standards established for infringement by mere protein mutants, they are even more obliged to apply this standard for in-

934 Betaseron was invented by David Mark, Leo Lin and Shi-Da Yu Lu at Cetus Corporation in the early 1980s. See. U.S. Patent No. 4,588,585 (issued May 13, 1986). The new drug based on a thin analog was approved by the Food and Drug Administration (FDA) for the treatment of relapsing-remitting multiple sclerosis in 1993. See FDA Press Release, FDA Licenses Interferon Beta-1b (July 23, 1993), available at http://www.fda.gov /gov/bbs/topics/new00424.html, last checked September 18, 2004. Betaseron is currently produced by Chiron Corporation and sold by Berlex Laboratories.

935 See Humalog (Inslulin lispro Injection) Prescribing information (May 1, 2000), available at http://pi.lilly.com/human-prescribing.pdf; TNKase (Tenectephase) Prescribing Information (June 2000), available at http://www.gene.com/gene/products/information/pdf/tnkase-prescribing.pdf, Infergen (Interferon alfacon-1) Prescribing Information (Nov. 30, 1998), available at http://208.254.60.143/md/pi/pi.htm., last checked September 18, 2004.

936 Ryan, L. Antony/Brooks, Roger G., Innovation vs. Evasion: Clarifying Patent Rights in Second-Generation Genes and Proteins, 17 Berkeley Tech. L.J. 2002, 1265, 1270.

937 Ahrer, Karin; Jungbauer, Alois, Chromatographic and electrophoretic characterization of protein variants, 841 Journal of Chromatography, Issues 1-2 (2006).

938 Holman, Christopher M., Protein similarity score: a simplified version of the blast score as a superior alternative to percent identity for claiming genuses of related protein sequences, 21 Santa Clara Computer & High Tech. L.J. 2004, 55, 59.

939 Friedberg, Iddo/Margalit, Hanah, Persistently conserved positions in structurally similar, sequence dissimilar proteins: roles in preserving protein fold and function, 11 Protein Science 2002, 350, 350.

fringement when it comes to entirely different polypeptide chains that are able to perform the patented effect.

Furthermore, knowledge regarding 3-D protein structure generally has practical value in protein engineering. The increasing information on 3-D structural features substantially facilitates the production of protein variants. In the past, engineers had access solely to primary structure-related information. For decades, prior art had included knowledge regarding which amino acid amendments could be made without influencing the ultimate effect of the protein. Nevertheless, improved understanding of 3-D folding types enables scientists to further classify existing knowledge. With the ultimate effect of a protein depending on the tertiary structure, more exact determinations are possible. In order to design and optimize enzymatic function, the engineer combines different protein structural features. The increased availability of 3-D structure knowledge now enables rapid improvement in the field of protein engineering.[940]

Therefore, it is possible to arrive at the preliminary conclusion that the standards developed for infringement related to protein variants are also suitable for establishing infringement by different proteins with structural similarities. It is, however, possible that modifications to existing categories are necessary. The following analysis will take a critical look at the applicability of protein variant procedure, and show in which cases they have to be adjusted. First, literal infringement is considered. Second, infringement under the doctrine of equivalents will be analyzed.

2. Literal infringement

a) Treatment of protein variants in the U.S.

In the case of the scope of protection of biotechnological inventions, one of the most fundamental questions is whether the use of a sequence dissimilar protein sharing common folds and function infringes the original protein patent. To answer this question one has to start by analyzing what an original patentee must include in his claim language in order to protect himself from competitors using the sequence-dissimilar protein. One form of protection could be to include the protein's function in the claim. Whether this is possible, and how much such an inclusion is interpreted as limiting the scope of the patent depends on existing case law related to protein inventions. The following paragraphs will examine cases related to protein inventions, consider how protection from "second-generation" analogs[941] can be established, and derive some basic principles. As a second step, the study will apply the principles and particularly consider how protection from "second-generation" ana-

940 For advances in 3D protein research and analysis, see Chapter 2 B II and Chapter 2 E II 2.

941 Ryan, L. Antony/Brooks, Roger G., Innovation vs. Evasion: Clarifying Patent Rights in Second-Generation Genes and Proteins, 17 Berkeley Tech. L.J. 2002, 1265, 1265 refers specifically to the term of "second-generation proteins".

logs can be established. A third step will apply these principles developed in the field of protein variants to the case where sequence-dissimilar proteins are used to 'invent around' existing protein patents.

aa) Claims defining proteins in terms of function

Previously, claims defining the protein solely by its function have been allowed.[942] Frequently, this was all that was known about the protein, particularly in cases in which the DNA sequence encoding for the protein had yet not been disclosed. Functional claims resulted in a broad patent coverage that also included variants performing desired functions. If the only limitation is function, the claim automatically encompasses all variants that carry out such a function. This patent practice has changed and currently courts require at least some sort of structural definition or a physical characterization that goes beyond mere functional description of the protein.[943] A number of cases deal with the question of how proteins must be described. In *Genentech v. Wellcome,*[944]Genentech owned a patent on human tissue plasminogen activator protein (t-PA), and on a gene coding for that protein.[945] The claim was directed to a DNA isolate essentially constituting a DNA sequence encoding t-PA.[946] One of the two potential infringers, *Wellcome*, used met-t-PA, a product that differed by a single amino acid from native human t-PA, apparently as a result of a

942 A definition by function apparently continues to be sufficient for antibodies, a sub-category of proteins, see Noelle v. Lederman, 355 F.3d 1343, 1349 (Fed. Cir. 2004), ("as long as an applicant has disclosed a 'fully characterized antigen', either by its structure, formula, chemical name, or physical properties, or by depositing the protein in a public depository, the applicant can then claim an antibody by its binding affinity to that described antigen.")

943 Holman, Christopher M., Protein similarity score: a simplified version of the blast score as a superior alternative to percent identity for claimng genuses of related protein sequences, 21 Santa Clara Computer & High Tech. L.J. 2004, 55-98, 62-68, citing Amgen, Inc. v. Chugai Pharmaceutical Co., 927 F.3d 1200 (Fed. Cir. 1991); Ex parte Maizel, 27 U.S.P.Q. 2d (BNA) 1662 (B. Pat. App. Interferences 1992); Fiers v. Revel, 984 F.2d 1164, 1171 (Fed. Cir. 1993).

944 Genentech, Inc. v. Wellcome Foundation, 29 F.3d. 1555 (Fed. Cir. 1994).

945 Tissue plasminogen activator (tPA), also referred to as 'clot-busting drug', is a thrombolytic agent. It is used for patients having a heart attack or stroke. The drug dissolves blood clots, which cause most heart attacks and strokes. A detailed description is available at http://www.americanheart.org/presenter.jhtml?identifier=4751, last checked on January 21, 2008. A good explanation related to the properties of a "human tissue activator" is also provided by the CAFC decision itself. Genentech, Inc. v. Wellcome Foundation, 29 F.3d. 1555, 1557 ("The protein tissue plasmin ogen activator (t-PA) plays an important role in the dissolution of fibrin clots in the human body. The body forms such clots typically to breach a rupture in a blood vessel. When they are no longer needed, they are dissolved through the action of plasmin, an enzyme which binds to the fibrin and severs the bonds between the fibrin molecules. Since plasmin circulates through the blood in an inactive form called plasminogen, a mechanism must be provided to activate the plasminogen and convert it to plasmin when a clot is targeted for dissolution by the body. The protein t-PA serves as that mechanism.")

946 Genentech, Inc. v. Wellcome Foundation, 29 F.3d 1555, 1558.

cloning error. The second competitor, Genetic Institute, utilized a product called FE1X, which lacked two of the five domains of the t-PA amino acid sequence and had two specific amino acid substitutions.[947]

The court held that the question of whether the structurally distinct proteins fall within the scope of the claim depends on the meaning of the phrase "human tissue plasminogen activator". Interpreting the claim, the Federal Circuit found that there were four possible definitions of the phrase set forth in the specification. First, there was a narrow structural definition limited to the amino acid sequence of neutral t-PA. Furthermore, two broader structural definitions were disclosed that provided information of particular regions known to be essential for biological activity. Finally, a functional definition was contributed that covers any protein with the characteristic biological activity.[948] The court stated that the first and most narrow definition was exclusively suitable for claim construction, since the others "cover an infinite number of permutations of natural t-PA". It held that the specification does not satisfy the enablement requirement under Section 112 in terms of the broader definitions. Therefore, the court concluded that the phrase "human tissue plasminogen activator" means natural t-PA. Since FE1X is not a naturally occurring variant of the full-length sequence of human t-PA, it is not covered by the patent scope.[949]

In *Amgen, Inc. v. Chugai Pharmaceutical Co.*, the claims were directed to a DNA sequence encoding a protein having an amino acid sequence "sufficiently duplicative" of erythropoietin to possess ''Epo's'' biological property of causing an increased production of red blood cells. [950] The court held one of the claims invalid due to a lack of enablement, finding that an endless number of possibilities for changing the 'Epo' structure existed. In addition, the court concluded that Amgen failed to provide sufficient structural information to produce analogs carrying out 'Epo'-like activities.[951]

In *Ex parte Maizel*[952], the invention involved the amino acid sequence of a B-cell growth factor. The claims described a DNA vector encoding a protein consisting of the claimed amino acid sequence or a "biologically functional equivalent thereof".[953] The Board of Patent Appeals held the claims invalid, reasoning that the term "biological functional equivalent thereof" may cover any conceivable means that brings

947 Genentech, Inc. v. Wellcome Foundation, 29 F.3d 1555, 1557.
948 Genentech, Inc. v. Wellcome Foundation, 29 F.3d 1555, 1563-1564.
949 Genentech, Inc. v. Wellcome Foundation, 29 F.3d 1555, 1560. The holdings may be questionable in light of the Federal Circuits's en banc holding in Phillips. The Court focused on the methodology of claim interpretation and strongly suggested that construing claims narrowly to avoid invalidity should occur only when other means of determining claim scope were unavailable. Thus, the Court's decision in Genentech to adopt the narrow construction, limited to the specific amino acid sequence, contrary to the broader generic intent, may not be followed in the future, see Phillips v. AWH Corp., 415F.3d 1303, 1313 (Fed. Cir. 2005) (en banc).
950 Amgen, Inc. v. Chugai Pharm. Co., 927 F.2d 1200, 1203 (Fed. Cir. 1991).
951 Amgen, Inc. v. Chugai Pharm. Co., 927 F.2d 1200, 1217.
952 Ex parte Maizel, 27 USPQ2d 1662 (P.T.O. Bd.Pat.App. & Int. 1992).
953 Ex parte Maizel, 27 USPQ2d 1662, 1663.

about the desired biological result. The specification did merely disclose a specific DNA sequence known to the patentee.[954]

In *Fiers v. Revel,* a claim intended to cover all DNA molecules coding for beta-interferon.[955] The court held that the patent did not meet the written description requirement, because it failed to provide a "precise definition, such as by structure, formula, chemical name or physical properties".[956] The above discussed[957] decision of *Regents of the University of California v. Eli Lilly and Co.*[958] further determined the standards for protein claims, reasoning in favor of structural definitions for amino acid sequences. As explained above, the invention involved claims to genes encoding mammalian insulin, while the patent description merely disclosed rat insulin cDNA. The patent was therefore held to be invalid, because it failed to provide the required "separate written description requirement". The case was distinguished from the established practice of determining a broad chemical genus by means of a generic formula. The court held that the claims at issue defined the genus by its function without describing any functional properties commonly possessed by members of the genus that distinguish them from others.[959]

bb) The USPTO Guidelines for Examination of the 'Written Description Requirement'

Despite extensive discussion surrounding the *Lilly* decision and its reasoning regarding a 'separate written description requirement', this case is frequently cited.[960] In response, the USPTO even changed its general practice, drafting the "Guidelines for Examination of Patent Application under the 35 U.S.C. 112, P1 'Written Description Requirement'"[961] and a "Synopsis of Application of Written Description Guidelines" (further referred to as "guidelines")[962]. The latter apply the standard of a "separate written description requirement" to a number of claims involving biotechnological

954 Ex parte Maizel, 27 USPQ2d 1662, 1665.
955 Fiers v. Revel, 984 .F2d 1164 (Fed. Cir. 1993).
956 Fiers v. Revel, 984 .F2d 1164, 1171.
957 Chapter 3 A III 1 c) bb).
958 Regents of the University of California v. Eli Lilly and Co., 119 F.3d 1559 (Fed. Cir. 1997).
959 Regents of the University of California v. Eli Lilly and Co., 119 F.3d 1559, 1566.
960 For example in Capon v. Eshhar, 418 F.3d 1349, 1355 (Fed. Cir. 2005); Moba, B.V. v. Diamond Automation, Inc., 325 F.3d 1306, 1320 (Fed. Cir. 2003); Hoffmann-La Roche, Inc. v. Promega Corp., 323 F.3d 1354, 1368 (Fed. Cir. 2003); Amgen Inc. v. Hoechst Marion Roussel, Inc., 314 F.3d 1313, 1331 (Fed.Cir. 2003).
961 "Guidelines for Examination of Patent Application Under the 35 U.S.C. 112, P1 'Written Description Requirement'", 66 Fed. Reg. 1099 (Jan 5, 2001).
962 United States Patent and Trademark Office, Synopsis of Application of Written Description Guidelines, 1997, available at http://www.uspto.gov/web/menu/written.pdf, last checked on January 21, 2008.

material.[963] Although the guidelines must be understood as a mere administrative framework, courts frequently rely upon them. In *Enzo II*,[964] the Federal Circuit court found that the DNA-related invention had to be rejected under the Written Description Guidelines. The lower district court on remand was appointed to precisely apply the USPTO guidelines to the claims.[965] In *Noelle v. Lederman*,[966] the CAFC went even further, stating that an example in the guidelines directed to a hypothetical antibody claim must be considered as precedent. Relying upon this example, the claim at issue was held to be invalid. The court concluded the example to be precedent on grounds of that it had been cited in *Enzo II*, even though *Enzo II* had only referred to the example with regard to the general USPTO written description practice.[967]

The guidelines provide information regarding the amount of sequences that must be disclosed in order to satisfy the written description requirement. A genus is understood as a group of species defined by similar sequences. Example 13 of the guidelines demonstrates the following claims:

1. An isolated protein having SEQ ID NO:3

2. An isolated variant of the protein of Claim 1.[968]

Regarding Claim 1 the guidelines determine that "the single disclosed example is representative of the claimed genus. In view of pre-existing knowledge, the disclosure is sufficient to show that one of skill in the art would conclude that the applicant was in possession of the claimed genus." In contrast, Claim 2 fails to meet the standard established by the guidelines. They do not allow recitation of a specific sequence and to claim it and its functional variants. In this context, it is held that "the specification and claim do not indicate what distinguishing attributes are shared by the members of the genus". Thus, it is argued that no structural properties are indicated which distinguish compounds in the genus from others in the protein class.[969]

The guidelines further demonstrate that it is possible to claim a genus of protein variants sharing similar sequences and common functionality. Applying this principle Example 14 of the guidelines represent the following claim:

963 As explained earlier, some of the Judges of the Federal Circuit also apply a "separate written description requirement." For decisisve cases and the debate surrounding these decisions, see Chapter 3 A III 1 c).

964 Enzo Biochem, Inc. v. Gen-Probe Inc., 323 F.3d 956 (Fed. Cir. 2002) (Enzo II)).

965 Enzo Biochem, Inc. v. Gen-Probe Inc., 323 F.3d 956, 968.

966 Noelle v. Lederman, 355 F.3d 1343 (Fed. Cir. 2004).

967 Noelle v. Lederman, 355 F.3d 1343, 1348.

968 United States Patent and Trademark Office, Synopsis of Application of Written Description Guidelines, 1997, 50, available at http://www.uspto.gov/web/menu/written.pdf, last checked on January 21, 2008.

969 United States Patent and Trademark Office, Synopsis of Application of Written Description Guidelines, 1997, 51-52, available http://www.uspto.gov/web/menu/written.pdf, last checked on January 21, 2008.

> A protein having SEQ ID NO: 3 and variants thereof that are at least 95% identical to SEQ ID NO: 3 and catalyze the reaction of A-B (a functional characteristic of SEQ ID NO: 3.[970]

The guidelines explain that "procedures for making variants of SEQ ID NO: 3 which have 95 % identity to SEQ ID NO: 3 and retain its activity, are conventional in the art". Further, it is found that "substantial variations" among the members of the genus do not exist, "since all of the variants must possess the specified catalytic activity.[971]

Subsequent case law, however, questions whether the Court's decision to adopt the narrow construction established in *Lilly*, namely limited to the specific amino acid sequence, should be observed. For example, the CAFC in *Capon v. Eshhar*, a decision that involved chimeric DNA claims, found that the written description requirement of 35 U.S.C. §112 paragraph 1 does not impose a *per se* rule that the specification must recite the nucleotide sequence of claimed DNA when that sequence is already known in the field.[972] The court reasoned that "the law must take cognizance of the scientific facts" and that the "written description" requirement must be applied in the context of the particular invention and the state of the knowledge".[973] From the Court's view, "the predictability or unpredictability of the science is relevant to the decision as to how much experimental support is required to adequately describe the scope of the invention."[974] The court explained that

> "[T]he "written description" requirement states that the patentee must describe the invention; it does not state that every invention must be described in the same way. As each field evolves, the balance also evolves between what is known and what is added by each inventive contribution."[975]

Notwithstanding the decision of *Capon v. Eshhar,* which will again be addressed in the context of defining a protein by its folding type, the law clearly requires more than a mere functional definition of proteins. The "percent identity approach" suggested in the guidelines is also conventional U.S. patent granting practice. Large numbers of patents have been issued, such as U.S. Patent No. 6,930,085 claiming orally administrable peptides that ameliorate symptoms of atherosclerosis. [976] Claim 2 of this patent, owned by "The Regents of the University of California", encompasses a specific polypeptide wherein said peptide shows greater than approximately

970 United States Patent and Trademark Office, Synopsis of Application of Written Description Guidelines, 1997, 53; available at http://www.uspto.gov/web/menu/written.pdf, last checked on January 21, 2008.

971 United States Patent and Trademark Office, Synopsis of Application of Written Description Guidelines, 1997, 53-53, available at http://www.uspto.gov/web/menu/written.pdf, last checked on January 21, 2008.

972 Capon v. Eshhar; 418 F.3d 1349, 1358 (Fed. Cir. 2005).

973 Capon v. Eshhar; 418 F.3d 1349, 1357.

974 Capon v. Eshhar; 418 F.3d 1349, 1360.

975 Capon v. Eshhar; 418 F.3d 1349, 1358.

976 U.S. Patent No. 6,930, "G-type peptides to ameliorate atherosclerosis", by Fogelman, Alan M./Navab, Mohamad, Oakland, CA 2005.

50% sequence identity with Apolipoprotein J.[977] Proteins defined by the percent identity method typically recite a "reference sequence" and a specified percent identity. Thereby, a genus of polypeptide sharing some minimal threshold of sequence identity with another is determined. Most patents involving percent identity claims will provide some definition of the term "identical". A typical definition, such as provided by the "085 patent" states that percent "identity" refers to sequences or subsequences that are the same or have a specified percentage of amino acid residues that are the same, when compared and aligned for maximum correspondence, as measured using a specific sequence comparison algorithm.[978]

b) Treatment of protein variants in Germany

As in the U.S., the German standards developed for protein variants may satisfy the treatment of dissimilar proteins bearing structural similarities. In Germany, it is also an established practice to read claims to cover protein variants.[979] This practice is justified by the common knowledge that not every amendment of a provided sequence necessarily results in loss of the designated function. There are many known proteins in which a sequence variation has either minimal, or no effect at all.[980] It is known by the prior art that certain amino acid amendments can be made without influencing the final effect of the protein. Protein variants claims include alleles or derivatives having emerged from amino acid deletion, substitution, insertion, inversion, addition or exchange.[981] There are basically four different classes of amino acids determined by different side chains: (1) non-polar[982] and neutral (Alanine, Valine, Leucine, Isoleucine, Proline, Phenylalanine, Methionine, Tryptophane), (2) po-

977 Apolipoprotein J (apo J) is a protein used in the pathogenesis of Alzheimer; see Glossary of The Biotechnology Institute, available at http://www.biotechinstitute.org/what_is/glossary.html, last checked on January 21, 2008.

978 Fogelman, Alan M./Navab, Mohamad, G-type peptides to ameliorate atherosclerosis, Oakland, CA 2005; see also Holman, Christopher M., Protein similarity score: a simplified version of the blast score as a superior alternative to percent identity for claimng genuses of related protein sequences, 21 Santa Clara Computer & High Tech. L.J. 2004, 55-98, 69 citing U.S. Patent No. 6,657,047 as another example of a claim defining a protein genus in terms of percent identity.

979 OLG Düsseldorf vom 10.02.2005, I-2 U 80/02, N. Publ. The threshold is what was foreseeable by a person skilled in the art to be covered by the patent claim; in the case of antibodies, a skilled person was not able to foresee that recombinantly produced human antibodies were included in a claim directed to murine antibodies.

980 U.S. Patent 6403764 "Insulin-like growth factor-1 protein variants" by Dubaquie, Yves, Fielder, Paul J., Lowman, Henry B., CA 2002.

981 Meyer-Dulheuer, K.-H., Der Schutzbereich von auf Nucleotid- oder Aminosäurensequenzen gerichteten biotechnologischen Patenten, GRUR 2000, 179, 180.

982 Nonpolar refers to covalent bonds in which electron density is symmetrically distributed, see The Chemical Glossary, at http://www.allchemicals.info, last checked on January 21, 2008.

lar[983] and neutral (Glycine, Asparagine, Glutamine, Cysteine, Serine, Threonine and Tyrosine), (3) acidic[984] and polar (Asparagine, Glutamate), and (4) basic[985] and polar (Lysine, Arginine, Histidine).[986] Due to the similarities within one group, it can be predicted that the replacement of one group member (e.g. Leucine through Isoleucine or Valine, the replacement of Asparagine through Glutamate or the replacement of Threonine through Serine) results, with a high predictability, in a protein with similar effects.[987] Thus, the inventor of a novel sequence is entitled to articulate claims involving such sequence variants.

No German cases could be found that deal with the treatment of claims directed to protein variants. However, an unpublished decision from the Düsseldorf Court of Appeals can provide guidance on their likely treatment.[988] In *Pro-Urokinase* the patent at issue claimed a thrombolytic with plasminogen activator isolated from urine. The urine consisted of urokinase characterized by a certain molecular weight. The allegedly infringing embodiment was a pro-enzyme with a single-chain protein structure bearing a sequence of 411 amino acids without attached sugar residues derived from a human pharynx carcinoma cell line. The court found that claim 1 consisted of a number of identifying parameters, some of which were of subsidiary importance. The court acknowledged that the allegedly infringing product was "chemically and in patent-law terms a different product" than the patented product, because it lacked a glycoside-sidechain. Nevertheless, the court found that the patent was infringed under the doctrine of equivalents. The court held that a person skilled in the art would have known from the patent specification that any sugar-free high-molecular single-chain urokinase achieved the same effect as the patented product. The court held that the crucial question was whether a person skilled in the art was able to understand from the patent disclosure that the allegedly infringing product could be used to replace the patented product while achieving the same effect. The glycosylation was the only difference between the parameters described in the patent claims and the allegedly infringing embodiment. Neither the claim, nor the description, the court found, mentioned that an addition of a sugar molecule was significant. The patent description rather disclosed the single-chain nature as key element of the product. Therefore, the court concluded, a person skilled in the art would have easily recognized the insignificance of the attached sugar. He would either have concluded

983 Polar means a covalent bond with unsymmetrical distribution of electron density, see The Chemical Glossary, available at http://www.allchemicals.info, last checked on January 21, 2008.

984 Acidic side chains are side chains havinga negative charge under physiological conditions, Whitford, David, Proteins: Structure and Function, Chichester, West Sussex, U.K 2005, 25.

985 Basic refers to proteins with side chains consisting of a ionizable OH group, see The Chemical Glossary, available at http://www.allchemicals.info, last checked on January 21, 2008.

986 Whitford, David, Proteins, Structure and Function, Chichester, West Sussex, U.K 2005, 15.

987 Whitford, David, Proteins, Structure and Function, Chichester, West Sussex, U.K 2005, 24-25. See also PCT-Application WO93/08298, Soluble Variants of Type I Membrane Proteins, and Methods of using them, The Wistar Institute of Anatomy and Biology, 1993.

988 Düsseldorf, Court of Appeals, 2 U 52/89, N. Publ.

that the non-glycosylated protein could be considered thrombolic or derived from the claim language that the patented effect could be achieved from different glycosylation patterns.[989]

The decision shows that equivalency is determined from the perspective of the person skilled in the art. If he understood from the patent disclosure that same effects could be achieved[990] by a means other than the patented means, equivalency is constituted. This is typically the case if the structural variation is of no significance for the patented effect. As stressed by *Lederer*, this approach is consistent with the three "Improver Questions" established by English House of Lords:

> "1) Does the variant have a material effect upon the way the invention works? If yes, the variant is outside the claim. If no 2) Would this (i.e. that the variant had no material effect) have been obvious at the date of publication of the patent to a reader skilled in the art? If no, the variant is outside the claim. If yes 3) Would the reader skilled in the art nevertheless have understood from the language of the claim that the patentee intended that strict compliance with the primary meaning was an essential requirement of the invention? If yes, the variant is outside the claim."[991]

The application of the rules established in the field of chemicals to the issue of protein variants is justified. On the one hand, the inventor cannot be expected to test all structural elements at all possible positions in the molecule before filing a patent claim. The rule, on the other hand, that a person skilled in the art must understand from the disclosure that the allegedly infringing variant is achieving same effects sufficiently copes with the principle of legal certainty.

c) Application of the principles reliable for protein variants on the use of sequence-dissimilar proteins

Both the European and the U.S. system follow similar approaches with regard to protection from the use of protein variants. Under both laws, sequence similarity is used as a reference. But is this of any assistance for a patentee who seeks to protect himself from competitors using sequence-dissimilar proteins? Many dissimilar-sequence proteins share common folds without sharing any sequence homology. These proteins are not covered by a percent identity approach using the sequence as reference. But, how can an inventor broaden his patent coverage to other proteins sharing common functions? As explained above, to merely claim the function of the protein is no solution, because due to advances in protein research the law does not tolerate such a practice.[992] A definition based on the protein's function is consequently not a viable alternative. As discussed in chapter II, the folding type rather

989 OLG Düsseldorf, Pro-Urokinase, N. Publ.
990 21 IIC 860 (1990) – Epilady United Kingdom II.
991 Lederer, Franz, Equivalence of chemical product patents, 30 IIC 275, 277 (1999).
992 See Chapter 4 C IV 2 a) aa); also Amgen, Inc. v. Chugai Pharmaceutical Co., 927 F.3d 1200 (Fed. Cir. 1991); Ex parte Maizel, 27 U.S.P.Q. 2d (BNA) 1662 (P.T.O. Bd.Pat.App. & Int. 1992); Fiers v. Revel, 984 F.2d 1164, 1171 (Fed. Cir. 1993).

than the sequence dictates the protein's function.[993] Hence, if the protein is defined by its folding type, all sequence-dissimilar proteins bearing the same functions/effects are automatically included. The proteins' definition by folding type thus must be considered an alternative approach that appropriately provides protection from competitive use, and at the same time ensures adequate disclosure to society. Claims that follow this approach may either directly define the protein by its tertiary structure or include a percent identity that uses the folding type as a reference. The method used for protection against the competitive use of protein variants (percent identity with sequence reference) could thus be modified accordingly. As shown above, the USPTO guidelines, Example 13, suggest the following form for such claims:

> A protein having [SEQ ID NO: 3] and variants thereof that are at least 95% identical to [SEQ ID NO: 3] and catalyze the reaction of A-B (a functional characteristic of SEQ ID NO: 3).[994]

To enable the coverage of the folding type, the sequence reference must be replaced by a reference to the folding type. Such claim may read as follows:

> A protein having SEQ ID NO: 3 and [a folding type X] and variants thereof that are at least 95% identical to [a folding type X] and catalyze the reaction of A-B (a functional characteristic of SEQ ID NO: 3)

The suggested approach (percent identity with 3D folding type reference) warrants that advances in prior art accomplished by modern proteomics technologies directed to physical structure determination are adequately taken into account.

d) Analysis of the approach to define a protein by folding type and function

There might, however, exist certain practical difficulties in claiming a protein by its folding type. From a view that uses the 3-D protein folding structure as opposed to sequence, the sequence might have a number of advantages. First, an amino acid sequence is moderately stable; its form does not change depending on surrounding conditions such as temperature, chemical environment, or upon the binding of additional compounds. Further, it is moderately simple to express a sequence in terms of words entailing simple search and comparison of the prior art. Such an expression contains the advantage that the prior art can be more easily searched and compared. With regard to a 3-D protein structure, by contrast, the surrounding conditions, e.g., the temperature or other influencing circumstances, must also be included in the patent claim. With regard to infringement or validity of a patent, the examination of the 3-D folding structure might thus be much less certain compared to sequences. With regard to the concrete claim language, defining the "fold" for purposes of claiming involves a high level of complexity. While the amino acid is stable, 3-D protein conformation obviously fluctuates moderately. Consequently, an inventor

993 Chapter 2 B I 3.

994 See Chapter 4 C IV 2 a) bb), citing United States Patent and Trademark Office, Synopsis of Application of Written Description Guidelines, 1997, 53; available at http://www.uspto.gov/web/menu/written.pdf, last checked on January 21, 2008.

must include information as to how much a structure could vary from a reported structure and still fall within the claim.

The above cited decision of *Capon v. Eshhar*[995], however, provides some relief to inventors, since they do not have to disclose what is already established in the art. The court held that nucleotide-by-nucleotide re-analysis is not required when the structure of the component DNA segments has already been disclosed and determined by known methods.[996] The court also explained that it is "not necessary that every permutation within a generally operable invention" be elucidated in order to be effective for an inventor to obtain a generic claim, as long as the effect is sufficiently demonstrated to characterize a generic invention.[997] Altogether, the sufficiency of specification support must be determined on a claim-by-claim basis under the facts of the particular case. The "predictability or unpredictability of the science is relevant for deciding how much experimental support is required to adequately describe the scope of an invention".[998]

With regard to the initial question of how a claim can define a protein by its folding type, this means that a patentee is not required to provide a re-description of what is established in the art. Thus, if the specific effect of a surrounding condition to a claimed tertiary structure is already known in the art it must not be expressed in the patent. If scientists have already reported the extent to which a certain structure could vary from other reported structures, it is not necessary to include this information in the patent language again. In summary, the more advances in proteomics are achieved, the less a patentee is required to disclose in his patent. Consequently, the improvement of proteomics technology and its contribution to the state of the art will increasingly provide substantial relief to patentees seeking to obtain broad protein 3D structure claims.

Another practical difficulty with claiming a protein by its 3-D folding structure might, however, exist with regard to the prior art. If a patent defines a protein by a certain fold, there might be proteins in the prior art, but whose fold has not yet been determined or reported. The question thus emerges whether these prior art proteins anticipate the claim, e.g. render the claim invalid. The above-analyzed trilateral studies clearly indicated that the tertiary folding type can be patented, although corresponding proteins are already disclosed by their primary sequence, as long as the inventor proves that the tertiary folding type is the more reliable parameter than the primary sequence.[999]

In order to determine whether a protein 3D structure claim is anticipated, the examiner must be able to distinguish the 3-D structure of prior art proteins from the newly claimed protein folding structure. Therefore, it is necessary that the 3-D struc-

995 Capon v. Eshhar, 418 F.3d 1349 (Fed. Cir. 2005)
996 Capon v. Eshhar, 418 F.3d 1349, 1358.
997 Capon v. Eshhar, 418 F.3d 1349, 1359.
998 Capon v. Eshhar, 418 F.3d 1349, 1360.
999 Chapter 3 B II 1 c).

ture for these prior art proteins was accurately determined previously. Otherwise, there would be no possibility for the examiner to make such a distinction.

In order to receive a patent to all proteins sharing a common fold, a patent applicant must describe a protein by its function. Therefore, it should be required to identify key residues in an active site, claim all proteins sharing a certain fold, and indicate the disposition of key functional groups in that structure.

Besides the practical difficulties that are likely to be manageable for sophisticated patent drafters, there seem to be no obstacles that would inherently prevent one from using the approach of defining a protein by its tertiary folding stage limited to a specific function. With regard to the scope of claims, an approach based on fold does clearly have some advantages over an approach based on sequence similarity. With the law expected to tolerate such claims, patentees should not hesitate to use it.

3. Infringement under the doctrine of equivalents

a) U.S.

aa) Methods for determining equivalents

Rather than seeking broad literal coverage, one might rely on the doctrine of equivalents to expand the claim coverage. This approach must be sharply distinguished from the above-described method. An inventor does not literally define a protein by its tertiary folding type, but rather solely by its sequence. The coverage towards sequence-dissimilar proteins sharing common functions might then be achieved by the doctrine of equivalents.[1000] The expansion of these rights under the doctrine of equivalents raises the question of their equitable nature. The question of expansion primarily depends on which method is applied for establishing equivalents. As set forth above, several approaches have been used in the U.S in order to determine equivalents. As a first step, it will be analyzed which of these methods is suitable for covering inventions involving 3-D protein structures. The analysis will particularly take into account the fact that – due to the advances in proteomics – prior art now includes substantial knowledge regarding protein folding properties and structures in

1000 Ryan, L. Antony/Brooks, Roger G., Innovation vs. Evasion: Clarifying Patent Rights in Second-Generation Genes and Proteins, Berkeley Tech. L.J., 17 Berkeley Tech. L.J. 2002, 1265, 1284. The Federal Circuit applied the doctrine of equivalents to a number of cases involving proteins, see Holman, Christopher M., Protein similarity score: a simplified version of the blast score as a superior alternative to percent identity for claimng genuses of related protein sequences, 21 Santa Clara Computer & High Tech. L.J. 2004, 55, 61 and the cited cases Amgen, Inc. v. Hoechst Marion Roussel, Inc., 314 F.3d 1313 (Fed. Circ. 2003); Genentech Inc. v. Wellcome Foundation, 29 F.3d 1555 (Fed. Circ. 1994).

general.[1001] Hence, the emerging question is how those developments influence the handling of legal categories such as the doctrine of equivalents.

i. The "Hypothetical Claim" Analysis

First, the 'hypothetical claim' approach is examined. The question raised in *Wilson Sporting Goods*[1002] is whether this hypothetical claim is anticipated by the prior art.[1003] If anticipation is established, it is improper to permit the patentee to enforce the patent under the doctrine of equivalents. If, by contrast, the hypothetical claim is patentable in the light of prior art, prior art does not bar the expansion of the claim under the doctrine of equivalents.[1004]

The method only introduces the framework of a new analytical technique, without considering the details of its application.[1005] It establishes a limitation of equivalents without providing detailed information regarding the exact determination of what is considered to be within the limits. The answer to the question of how equivalency is limited does not automatically provide information about how it is determined. A hypothetical claim will not anticipate the allegation of equivalents, particularly in protein science. A structurally similar protein or a protein variant will typically not be included in the prior art and thus not be anticipated or rendered obvious by the hypothetical claim. In many cases, the competitor using the structurally similar protein is the first to discover the structural similarity and the resulting effect. The same applies for the creator of a protein variant who, in many cases, is the first to modify the protein.[1006] Hence, the theory does not provide an adequate protection from competitors creating analogs or isolating structurally similar proteins with the purpose of copying existing drugs.[1007]

A number of authors suggested applying an "expanded hypothetical claim analysis" and to incorporate the requirement of Section 112.[1008] Such an approach shall

1001 Whitford, David, Proteins: Structure and Function, Chichester, West Sussex, U.K 2005, 39.

1002 Wilson Sporting Goods Co. v. David Geoffrey & Associates, 904 F.2d 677 (Fed. Cir. 1990), cert. denied, 111 S. Ct. 537 (1990).

1003 Wilson Sporting Goods Co. V. David Geoffrey & Assocs., 904 F.2d 677, 684 (Fed. Circ. 1990) (emphasis in original), cert. denied, 498 U.S. 922 (1990); see also K-2 Corp. v. Salomon S.A., 191 F.3d 1356, 1367 (Fed. Cir. 1999).

1004 Kushan, Jeffrey, Protein Patents and the Doctrine of Equivalents: Limits on the Expansion of Patent Rights, 6 Berkeley Technology Law Journal 1991, 108, 131.

1005 Parker, Hendrik D., Doctrine of Equivalents analysis after Wilson Sporting Goods: The hypothetical claim hydra, 18 AIPLA Quarterly Journal 1990, 262, 274.

1006 Ryan, L. Antony/Brooks, Roger G., Innovation vs. Evasion: Clarifying Patent Rights in Second-Generation Genes and Proteins, 17 Berkeley Tech. L.J. 2002, 1265, 1267.

1007 Ryan, L. Antony/Brooks, Roger G., Innovation vs. Evasion: Clarifying Patent Rights in Second-Generation Genes and Proteins, 17 Berkeley Tech. L.J. 2002, 1265, 1267.

1008 Sarnoff, Joshua, The Doctrine of Equivalents and Claiming the Future after Festo, 14 The Federal Circuit Bar Journal 2004, 403, 447. Although the Federal Circuit has held that the hypothetical claim construction is a useful tool, it has yet not required district courts to do

not only examine whether the hypothetical claim is anticipated by the prior art, but also whether the patent specification provides sufficient information to enable the scope of such a claim.[1009] This technique is not persuasive, either. First, it conflicts with the public dedication rule. According to this rule, subject matter disclosed in the specification, but not claimed, is dedicated to the public and thus not suitable for determining equivalents. The decisive elements for the interpretation of patent claims are the claims themselves. Further, the test shifts the burden of proof for infringement. Usually, the patentee must prove infringement. Applying this principle under the doctrine of equivalents means that the patentee must prove that the prior art does not bar the asserted equivalents. Under the hypothetical claim analysis, the patentee has to prove the validity of the hypothetical claim. According to the statutory presumption of validity, however, the patentee is usually not obliged to prove the validity of the asserted claim. Instead, an asserted infringer carries the burden of proving the affirmative defense of invalidity of the asserted claim. If the hypothetical claim test requires that the patentee must prove the validity of the hypothetical claim, the interpretation that the patentee must also prove the validity of the asserted claim may be assumed. Introducing another preliminary and subsidiary validity analysis with respect to a second claim not actually present is not helpful for an exact examination in trial.[1010] Rather than clarifying the analysis of equivalents, the test leaves many questions open, in particular regarding the treatment of structurally similar proteins or protein variants.

For all these reasons, the hypothetical claim analysis is not an appropriate method for coping with the new challenges arising from advances in protein engineering and in the field of proteomic inventions.

ii. The interchangeability test

In addition, the 'insubstantiality of differences test' will be evaluated. The question raised in *Graver Tank & Manufacturing Co. v. Linde Air Products Co.*[1011] was "whether persons reasonably skilled in the art would have known of the interchangeability of an ingredient not contained in the patent with one that was".[1012] Accord-

so; for a more detailed description see Siekman, Michael T., The Expanded Hypothetical Claim Test: A Better Test for Infringement for Biotechnology Patents under the Doctrine of Equivalents, Boston University Journal of Science and Technology Law 1996, 6-12.

1009 Ryan, L. Antony/Brooks, Roger G., Innovation vs. Evasion: Clarifying Patent Rights in Second-Generation Genes and Proteins, 17 Berkeley Tech. L.J. 2002, 1265, 1287.

1010 Parker, Hendrik D., Doctrine of Equivalents analysis after Wilson Sporting Goods: The hypothetical claim hydra, 18 AIPLA Quarterly Journal 1990, 262, 275.

1011 Graver Tank & Manufacturing Co. v. Linde Air Products Co. 339 U.S. 605 (1950).

1012 Graver Tank & Manufacturing Co. v. Linde Air Products Co. 339 U.S. 605, 609.

ing to *Hilton Davis*[1013], this test had to take additional circumstances into account than the 'function-way-result' test, which was considered to be insufficient.

As for proteins, the method attempts to determine whether the function of two proteins differs. A protein is "interchangeable" if a person skilled in the art is relatively indifferent as to which one he would use. If, on the other hand, the skilled artesian prefers one protein, particularly due to its biological function, "interchangeability" is denied and equivalents are rejected. This test, however, is not suitable for coping with the challenges of modern protein design and drug development. The approach of distinguishing a protein merely on the level of its end function brings certain risks. Differences with regard to long term- and side effects may not be taken into account since the statement of one skilled in the art may very often not include any long-term research. Generally, a precise analysis of a protein cannot be made without examining the "way" in which a particular function is performed.

Protein functions mainly depend on the proteins' 3-D folding structure. In order to distinguish the end function precisely, an accurate understanding of slight differences within these structures is important. Even though the end function might only differ slightly, the concrete binding activity of a particular binding pocket can vary greatly. In contrast, the mere comparison of protein function in a biological organism does not typically take the 3-D structure into account, but focuses on the end function. At a time in which protein analyses mainly focus on the disclosure and analysis of the tertiary folding structure, this method appears insufficient and imprecise.

iii. The 'function-way–result' test

Next, a closer look is taken at the 'function-way-result' test. This method establishes a detailed examination of how a particular function is performed by binding activity or administering techniques. The accused product infringes if it substantially performs the same function in substantially the same fashion to obtain the same result as the existing patent.[1014] Thus, the first step is to determine the 'function' that characterizes the patented gene or protein.

Commentators[1015] have complained that the elements of the function-way-result-test are not suitable for determining the scope of equivalents for biotechnology patents. First, sources of claim construction might refer both to broader and narrower "functions". Moreover, relying on the patent specification and prior art causes a

1013 Hilton Davis Chem. co. v. Warner-Jenkinson Co., 62 F.3d 1512, 1518-19 (Fed. Cir. 1995) (en banc), revised on other grounds, 520 U.S. 17 (1997).

1014 Sanitary Refrigerator Co. v. Winters, 280 U.S. 30, 42 (1929).

1015 Takenaka, Toshiko, Doctrine of Equivalents after Hilton Davis: a comparative law analysis, 22 Rutgers computer and technology law journal 1996, 479-520; Ryan, L. Antony/Brooks, Roger G., Innovation vs. Evasion: Clarifying Patent Rights in Second-Generation Genes and Proteins, 17 Berkeley Tech. L.J. 2002, 1265.

problem of timing. In *Warner-Jenkison v. Hilton Davis*, the Supreme Court held that equivalents must be examined at the time of infringement.[1016] If the question of "function" is analyzed, any properties of the patented gene or protein disclosed between the time of invention and the time of infringement are automatically considered irrelevant.[1017] Finally, critics allege that the test is problematic with regard to the "way" component. They assert that current scientific understanding of the way in which proteins perform their functions is not yet well advanced and often based on "trial and error" testing.

The criticism is not persuasive. According to Section 35 U.S.C. § 112 1, courts can only accept the functions that are enabled by the patent specification when they interpret claims. Regarding the way a certain function is performed, skilled artisans are commonly able to interpret the differences in the function of proteins. Although the exact folding structure might not be known, scientists may be familiar with folding groups, such as protein super families, and be able to determine the family to which the given protein belongs. It may also be possible to make statements concerning the amino acid sequences that play a critical role in folding at the tertiary level. With current developments in proteomics, whose goal is total disclosure of 3-D protein structures, difficulties with the 'function-way-result' test that may have existed in the past have been overcome. With proteomic researchers able to thoroughly determine 3-D protein structures, the test is in most cases easy to conduct.[1018] The method of analyzing the 'function', the 'way' and the 'result' of a protein thus leads to a very precise and accurate comparison of the native protein, its engineered analogs and dissimilar proteins with structural similarities. In particular, it is even possible to determine slight differences in binding activity and thus indicate long-term and side effects. The mode is therefore appropriate, suitable, and sufficient for determining equivalents with regards to inventions involving 3-D protein structure. In particular, it is adequate for the determination of whether the patent scope covering a protein extends to sequence-differing proteins sharing common fold and function.

bb) The ruling of *Genentech v. Wellcome* and the doctrine of equivalents

The above-mentioned[1019] decision of *Genentech v. Wellcome*[1020] encompasses a detailed analysis of how the doctrine of equivalents is examined according to the function-way-result test. The decision is of particular interest because the dissenting opi-

1016 Warner-Jenkison v. Hilton Davis, 520 U.S. 17, 19.

1017 Ryan, L. Antony/Brooks, Roger G., Innovation vs. Evasion: Clarifying Patent Rights in Second-Generation Genes and Proteins, 17 Berkeley Tech. L.J. 2002, 1265, 1286.

1018 Different view: Ryan, L. Antony/Brooks, Roger G., Innovation vs. Evasion: Clarifying Patent Rights in Second-Generation Genes and Proteins, 17 Berkeley Tech. L.J. 2002, 1265, 1287.

1019 Chapter 4 C IV 2a) aa).

1020 Genentech, Inc. v. Wellcome Foundation, 29 F.3d 1555.

nion closely questions the function-way-result test, asserting that it lacks the ability to cope with the challenges of protein engineering.[1021] In reviewing this major decision, the arguments used in the dissenting part will be evaluated. Moreover, it will be discussed whether they are of any value for the field of proteomic inventions.

After the examination of literal infringement, the court in *Genentech v. Wellcome* had to decide whether the "human tissue plasminogen activator limitation" appearing in the *Genentech* patent claims was met by an equivalent element of FE1X, the competitor's protein variant, under the doctrine of equivalents.[1022] Reviewing the claims, the court emphasized that the 'way' or 'result' prongs were highly dependent on the 'function' prong. The first important issue in the context of the "triple-test" of equivalency was thus "how broadly one defines the function of human t-PA".[1023] With the intended function viewed in the context of the patent, the prosecution history, and the prior art, the court concluded that the district court had interpreted the claim language too broadly. The 'function' of human t-Pa, rather, includes a 'fibrin binding' process. Such a narrow definition of the claim, however, "is devoid of any … linking argument showing that FE1X functions in substantially the same way as human t-PA or achieves substantially the same result".[1024] Furthermore, the court stated that existing testimony on the binding activity of the active centers was only vague and speculative. As a consequence of the deletion of the E and F regions in the protein variant, the binding affinity of FE1X must be considered to be substantially different from the natural protein.[1025] First, the mode of the protein variant's binding is different. Second, the protein variant behaves differently from human t-PA.[1026] The court furthermore relied on the decision of *Malta*[1027]acknowledging that the state of the science in this area of endeavor is very imprecise. Therefore, *Malta* could not be interpreted as requiring plaintiffs/appellees to prove more specific details of the binding mechanism to the different properties and structure of FE1X involved in the binding process.[1028] Nevertheless, the court could determine that by demonstrating that a certain region of the protein structure plays a role in the binding function of both the natural and the modified protein, compliance with the 'triple-test' was insufficient. The profound differences in the properties and structure possessed by each protein would not allow such an interpretation.[1029]

In the dissenting opinion,[1030] Judge Lourie asserted that the focus on the 'function, way-result' is undue. Especially when the patented material is chemical in na-

1021 Krefft, Alexander Richard, Patente auf human-genomische Erfindungen: Rechtslage in Deutschland, Europa und den USA, München 2003, 291.
1022 Genentech, Inc. v. Wellcome Foundation, 29 F.3d 1555, 1568.
1023 Genentech, Inc. v. Wellcome Foundation, 29 F.3d 1555, 1567.
1024 Genentech, Inc. v. Wellcome Foundation, 29 F.3d, 1555, 1568.
1025 Genentech, Inc. v. Wellcome Foundation, 29 F.3d 1555, 1568.
1026 Genentech, Inc. v. Wellcome Foundation, 29 F.3d, 1555, 1568-69.
1027 Malta v. Schulmerich, 952 F.2d 1320 (Fed. Cir. 1991).
1028 Genentech, Inc. v. Wellcome Foundation, 29 F.3d 1555, 1569.
1029 Genentech, Inc. v. Wellcome Foundation, 29 F.3d 1555, 1569.
1030 Genentech, Inc. v. Wellcome Foundation, 29 F.3d 1555, 1570.

ture, this "limited means of analysis" fails to fully elucidate the issue. Pursuant to his view, it is not clearly distinguishable whether the particular characteristics of each product are part of the 'way'-, 'result'- or 'function'-prong. It is insufficient to say that the 'triple-test' determines "how" a substance works instead of what it does. The "insubstantially change-test" would rather be the only adequate method for illustrating the scope of equivalents. Applying such a method, however, the judge also reversed the district court's decision and chose to deny an infringement under the doctrine of equivalents.[1031]

cc) Application of the 'function-way-result' test to the issue of sequence-dissimilar proteins

How are the principles established in *Genentech* applied with regard to the initial question of whether the use of sequence-dissimilar proteins infringes the patent to the native protein? The court in *Genentech* focused on the question of how much the structure of a protein can be altered without amounting to a different "way" of accomplishing its function. It concluded that no equivalency was present, reasoning that the two patents involved different ways and functions. A sequence dissimilar protein can be considered to satisfy the "way" prong of the function-way-result inquiry. A protein having a different fold, by contrast, must be considered to accomplish the function by a different "way". As for *Genentech's* case reliance on the *Malta* decision[1032] it cannot be said any more that the state of the art in the area of protein science remains imprecise.[1033] In the post-genomic era, physical methods of determining the 3-D of proteins have been highly improved. Due to advanced proteomic technologies, such as x-ray crystallography or NMR structure determination, scientists are now able to determine the structures of many proteins on a precise level. Considerable research has been performed about protein folding models and aligned identical residues in sequence-dissimilar proteins sharing common folds. It is thus highly appropriate to require patentees to generate this information.[1034]

1031 Genentech, Inc. v. Wellcome Foundation, 29 F.3d 1555, 1568.

1032 Malta v. Schulmerich, 952 F.2d at 1327.

1033 The consideration of prior art is also required in light of the above-cited Capon v. Eshhar case, where the court reasoned that the "law must take cognizance of the scientific facts", see Capon v. Eshhar; 418 F.3d 1349, 1376 (Fed. Cir. 2005).

1034 The 'function-way-result' method had been applied by various other cases, e.g. Hughes Aircraft Co. v. United States, 86 F.3d 1566, 1584 (Fed. Cir.1996), remanded, 520 U.S. 1183, 117 S.Ct. 1466, 137 L.Ed.2d 680 (1997), aff'd, 140 F.3d 1470, reh'g denied, 148 F.3d 1384 (Fed.Cir.1998), cert. denied, 525 U.S. 1177, 119 S.Ct. 1112, 143 L.Ed.2d 108 (1999) (The patent at issue involved a method of keeping satellites properly aligned with the sun so to keep batteries loaded at any time. Years later the technology was computerized and put on the satellite itself. The Federal Circuit ruled that an inventor is not required to predict all future developments that enable the practice of his invention and therefore concluded infringement of this "later-arising technology" under the doctrine of equivalents. The conclusion was drawn by analyzing whether both inventions were operated by the same function,

dd) Expansion of the patent coverage to as yet unidentified species

The initial question has been whether an inventor is able to extend a claim defining the protein by sequence and function to sequence-dissimilar proteins sharing common effects by relying upon the doctrine of equivalents. With these proteins typically being unknown at the time the patent is issued, it must be asked whether patent claims can be interpreted broadly enough to encompass alternative, as yet unidentified, species. With later-discovered sequence-dissimilar proteins sharing common folds and effects representing a new technological means that is able to achieve same effects than an earlier patented technological means, it must be asked whether a patent involving a disclosed technology equivalently expands to later-arising technologies. To answer this question, one must precisely consider the legal limitations of the doctrine. As explained earlier,[1035] reliance upon equivalents is excluded if prosecution history estoppel applies. This rule basically states that a patentee cannot recapture through equivalents what he has surrendered during patent prosecution.[1036]

What is the relevance of this limitation in the context of the initial question, e.g., with regard to whether a patentee is able to claim as yet unidentified species bearing the same/similar folding type and function? Narrowing amendments are usually made in cases in which the patent offices find a claim too broad, e.g., not sufficiently supported by the patent description. Thus, they typically occur in cases in which a patentee attempts to claim unidentified species yet unknown at the time the patent application is filed.[1037] In this respect, it must be asked whether a narrowing amendment of protein function claims results in blocking a patentee from equivalently claiming yet undiscovered sequence-dissimilar, and structure-similar proteins. The question of whether a patentee may prove equivalents even though he narrowed the claim during the application process is of major interest for 3-D protein structure related inventions. [1038] As set forth above, the more recent *Festo* litigation abolished the earlier 'complete bar' rule and developed the 'flexible bar' approach.[1039] The de-

way and result. The case is considered a landmark for determining that the patent scope may encompass subsequent advances in prior art.

1035 Chapter 4 B I.

1036 Bergen-Babinecz, Katja/Hinrichs, Nikolaus/Jung, Roland/Kolb, Georg, Zum Schutzbereich von US-Patenten: Festo und eine deutsche Sicht, GRURInt. 2003, 487, 490.

1037 Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co., Ltd., 535 U.S. 722 (2002).

1038 To a certain point, the above-cited Genentech case already anticipated the revised Festo standards by demonstrating that a patentee who narrows an originally broad claim to a protein defined by function during prosecution history is not allowed to extend the patent scope beyond what was removed in the application process. The decision shows that a patentee cannot rely on the doctrine of equivalents for a scope of protection that encompasses subject matter deliberately removed from examination by the PTO during prosecution through narrow claiming. Having narrowed the claim during prosecution history, Genentech is not allowed to extend the patent scope beyond what was removed in the application process, see Genentech, Inc. v. Wellcome Foundation, 29 F.3d at 1557.

1039 In particular 'Festo VIII' where the Supreme Court disagreed with the 'complete bar' rule develped by the CAFC, setting forth a 'flexible bar' approach (Festo Corp. v. Shoketsu Kin-

cision of *Festo VIII* clearly determines when such a rule allows a patentee to claim equivalents, despite surrendering of parts of the original scope during prosecution.[1040] According to the Federal Circuit's complete-bar rule, the first goal of the history estoppel is "to hold the inventor to the representations made during the application process".[1041] By narrowing the content of a patent application, the patentee accepts that the patent does not extend as far as the original claim. The Supreme Court, however, held that this does not result in a precise drafting of the claim language such that a reliance on equivalency *per se* becomes unnecessary.[1042] The Court explains that:

> "[T]he narrowing amendment may demonstrate what the claim is not; but it may still fail to capture precisely what the claim is. There is no reason why a narrowing amendment should be deemed to relinquish equivalents unforeseeable at the time of the amendment and beyond a fair interpretation of what was surrendered. Nor is there any call to foreclose claims of equivalents for aspects of the invention that have only a peripheral relation to the reason the amendment was submitted. The amendment does not show that the inventor suddenly had more foresight in the drafting of claims than an inventor whose application was granted without amendments having been submitted."[1043]

The decision clearly explains that a patentee may prove equivalents for elements that have been unforeseeable at the time of the amendment. Thus, technology established at a later date is equivalently included, whereas previously established techniques that were not literally specified are not.[1044] The rational behind this finding is that patentees should not be punished for their inability to claim later-arising technology. In this respect, Judge Rader in *Festo* explained:

> "[w]ithout a doctrine of equivalents, any claim drafted in current technological terms could be easily circumvented after the advent of an advance in technology."[1045]

zoku Kogyo Kabushiki Co., 535 U.S. 722 (2002)) and 'Festo IX' where the CACFC on remand examined the claims at issue in light of such a 'flexible bar' rule (Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co., Ltd., 344 F.3d 1359 (Fed. Cir. 2003)).

1040 Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co., 535 U.S. 722 (2002) (Festo VIII).

1041 Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co., 535 U.S. 722, 724.

1042 Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co., 535 U.S. 722, 738.

1043 Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co., 535 U.S. 722, 738.

1044 In Chiron Corp. v. Genentech, Inc., the court distinguished between "nascent technology" and "future technology", e.g. "technology that arises after the date of application."; see at: 363 F.3d 1247, 1254-1256 (Fed. Cir. 2004). For a profound description of this case see Sarnoff, Joshua, The Doctrine of Equivalents and Claiming the Future after Festo, 14 The Federal Circuit Bar Journal 2004, 403, 430.

1045 Festo VI, 234 F.3d 558, 619 (Fed. Cir. 2000) (Rader, J., concurring in part and dissenting in part). See also Festo IX, 344 F.3d ate 1359, 1376-77 (Fed. Cir. 2003) (en banc) (Rader, J., concurring) (arguing for the foreseeability standard to avoid disrupting patentees expectations regarding patent scope during prosecution). Opponents of this view, including Sarnoff in the above-cited article, argue that the fact that a patent's claims may be designed-around in the future represents neither a doctrinal rational to extend protection beyond the claimed invention nor an indication that such additional protection would be appropriate. Therefore, opponents argue that some additional fairness criterion should be required to justify protection for unclaimed or unclaimable later-arising equivalents; Sarnoff, Joshua, The Doctrine of

Hence, narrowing amendments of protein function claims do not impede a patentee to rely upon equivalents for yet undiscovered sequence dissimilar proteins that perform common functions. Reliance upon equivalents for already known sequence-dissimilar proteins, by contrast, would be excluded by prosecution history estoppel, provided that a patentee had surrendered the scope of claims during the prosecution process.

Another difficulty patentees claiming the folding type of a protein may encounter falls under the principle of public dedication. Broad generic references in the written description may dedicate the patented subject matter to the public. As explained in I. B., the disclosure-dedication rule requires a patentee who discloses specific facts to also claim it, and to submit these claims to such a broader subject matter for examination. Otherwise, disclosed facts are dedicated to the public and may not be recaptured by using the doctrine of equivalents.[1046] The question emerges as to whether generic disclosures in the patent specification, such as the description of a protein folding type result in that all members, including the as yet unidentified of this particular genus are automatically dedicated to the public.

The decision *PSC Computer Products, Inc. v. Foxconn International*[1047] explains that the question of what is dedicated to the public mainly depends upon how specific a disclosure in a written description must be. The Federal Circuit found that equivalents are barred to the extent that persons of ordinary skills in the art would be able to "identify the subject matter that had been disclosed and not claimed."[1048] This means that not only expressly, but also implicitly disclosed subject matter is dedicated. With regard to the initial question it has to be asked whether this implies a conflict with the doctrine of equivalents protection for later species of proteins having similar folding structures. According to the principles of public dedication, the answer depends on whether the yet unidentified species is included in the patent being claimed. Under the *PSC Computer* decision, a patent description that implicitly contains information to as yet unidentified species is already sufficient to exclude such information from patentability. Consequently, the genus must be disclosed in a manner that would suggest the disclaiming of alternative, as yet unidentified species.[1049]

Equivalents and Claiming the Future after Festo, 14 The Federal Circuit Bar Journal 2004, 403, 452.

1046 PSC Computer Products, Inc. v. Foxconn International, Inc., 355 F.3d 1353 (Fed. Cir. 2004).

1047 PSC Computer Prods, Inc. v. Foxconn Intern., Inc., 355 F.3d 1353 (Fed. Cir. 2004).

1048 PSC Computer Prods, Inc. v. Foxconn Intern., Inc., 355 F.3d 1353, 1360.

1049 PSC Computer Prods, Inc. v. Foxconn Intern., Inc., 355 F.3d 1353, 1360.

b) Germany

aa) Infringement under the doctrine of equivalents

How should a claim that is broad enough to cover common structural folds be written pursuant to German claim construction rules? In order to establish the decisive elements for construction, the principles for equivalent claim construction explained in Chapter IV B. 2. must be considered. In addition, a claim must be viewed in light of recent case law of the German Federal Supreme court related to the determination of equivalents. The decisions of *Plastic Pipe*[1050], *Custodiol* I[1051], *Custodiol II*[1052], *Cutting Blade I*[1053] and *Cutting Blade II*[1054] were related to the question of whether figures or measurements in a claim allow some degree of approximation (and if so, to what degree). As in the U.S., the German Federal Supreme Court explicitly emphasized that the principle of legal certainty requires that the semantic content of the patent claims establish not only the starting point but also the decisive basis for determining the extent of protection.[1055] The following analysis will particularly focus on the *Cutting Blade* decisions. In *Cutting Blade I*[1056] the court stated in this context that

"if an embodiment departing from the essential meaning of the patent claim is to be included within the extent of protection, it is not sufficient that (1) it solves the problem underlying the invention with modified but objectively equivalent means and (2) that the person skilled in the art is able to use his specialist knowledge to identify the modified means as having the same effect. Just as the same effect cannot be found without focusing on the patent claim, (3) the considerations that the person skilled in the art must apply must in addition be focused on the essential meaning of the technical teaching protected in the patent claim in such a way that the person skilled in the art regards the different embodiment with its modified means as being equivalent to the solution in question."[1057]

Hence, an ordinary person skilled in the art has to define the scope beyond the wording of the protection based on the claim language. But to what extent is a patent used, and infringement established? In order to answer this question, it is necessary to first determine the content of patent claims, i.e., the semantic meaning attached to the claim language. If the contested embodiment uses the essential meaning of the

1050 BGH, 34 IIC 302 (2003) – Plastic Pipe (Kunstoffrohrteil).
1051 BGH, GRUR 2002, 523 – Custodiol I.
1052 BGH, 34 IIC 197 (2003) - Custodiol II.
1053 BGH, 33 IIC 873 (2002) – Cutting Blade I (Schneidmesser I).
1054 BGH, GRUR 2002, 519 – Cutting Blade II (Schneidmesser II).
1055 BGH, 33 IIC 873, 874 (2002) – Cutting Blade I (Schneidmesser I); Meier-Beck, Peter, Aktuelle Fragen der Schutzbereichsbestimmung im deutschen und europäischen Patentrecht, GRUR 2003, 905, 906.
1056 As for the factual background, see, Geißler, Bernhard, Noch lebt die Äquivalenzlehre, GRURInt 2003, 1, 3.
1057 BGH, 33 IIC 873, 874 (2002) – Cutting Blade I (Schneidmesser I).

patent claim, infringement exists. In order to find that the modified means used in the contested embodiment has the same effect for the solution of the problem underlying the invention, the skilled person may combine considerations based on the essential meaning of the invention with his particular knowledge.[1058]

In determining whether a concrete feature of the contested embodiment is within the scope of the patent, the corresponding features of both substances must be analyzed. An extension of scope to a different means finally depends on whether the principle of legal certainty still allows, or requires, such an extension in order to provide an appropriate reward for the patent owner for his scientific efforts.[1059] Pursuant to the principle of legal certainty, it is not sufficient that an embodiment of the invention is solely included in the patent description, but not encompassed by the semantic meaning of the claims. The inventor who is able to describe essential characteristics in the description should also be able to draft his patent claims encompassing such knowledge.[1060]

As set forth in question 3) in *Cutting Blade I*, the determination of an ordinary person skilled in the art must be focused on the essential meaning of the technical teaching protected in the patent claim in a way such that a person skilled in the art regards the different embodiment with the modified means as being equivalent to the solution at issue.[1061] Hence, the reasoning of *Cutting Blade I* not only requires a concrete orientation on the semantic meaning of the patent claim, but also gives a closer definition of such orientation; the person skilled in the art must be able to predict and take into account the contested embodiment. "Being equivalent to the solution at issue" is not to be understood technically in a sense of solely obtaining equal effects. The term rather refers to the closeness of the skilled person's considerations to the patent claim, which determines whether the contested embodiment is covered by the semantic meaning of the claim language.[1062] A contested embodiment is not covered if the skilled person's considerations are completely unrelated to the patent claim language. Rather, it is already sufficient that one single embodiment of the variant has no relation to the patented characteristics.[1063] The German Federal Supreme Court applied this rule in *Custodiol II*.[1064] In this decision, the patent claim was directed to a protective solution for the prevention of ischaemic[1065] damage to the heart and kidneys, and it determined that such solution should contain 10 +/-2 mil-

1058 BGH, 33 IIC 873, 874 (2002) – Cutting Blade I (Schneidmesser I).
1059 Benkard/Scharen, EPÜ, Art. 69, No. 82.
1060 Benkard/Scharen, EPÜ, Art. 69, No. 84; Meier-Beck, Peter, Aktuelle Fragen der Schutzbereichsbestimmung im deutschen und europäischen Patentrecht, GRUR 2003, 905, 906.
1061 BGH, 33 IIC 873, 875 (2002) – Cutting Blade I (Schneidmesser I).
1062 BGH, 33 IIC 873, 877 (2002) – Cutting Blade I (Schneidmesser I).
1063 Meier-Beck, Peter, Aktuelle Fragen der Schutzbereichsbestimmung im deutschen und europäischen Patentrecht, GRUR 2003, 905, 908-909.
1064 BGH, 34 IIC 197 (2003) - Custodiol II.
1065 Local anemia (insufficient blood supply) results from vasoconstriction, thrombosis or embolism, see Hyper Dictionary, available at http://www.hyperdictionary.com/dictionary/ ischaemia, last checked on January 21, 2008.

limole of magnesium chloride. The defendant used a protective solution that differed from the patented solution by the fact that the solution only contained an amount of 4 mmol/1 magnesium chloride.[1066] The court ruled that the amount of 4 mmol/1 magnesium chloride instead lacked any relation to what was patented, i.e., to the 10+/-2 millimole magnesium chloride of the patented subject matter. Hence, the contested embodiment did not fall into the patent scope, irrespective of the fact that it could be used equally effectively of therapeutic treatment.[1067]

The question of whether the skilled persons' considerations are focused on the essential meaning of the patented teaching in such a fashion that he regards the different embodiment with its modified means as being equivalent to the solution in question (question 3) shows parallels to the *Catnic* case[1068]. The decision handeled down by the U.K. House of Lords that dealt with the legal situation in the U.K. at an earlier stage offers some observations on the determination of equivalents under English law. Although the German question is phrased differently than the British example ("[W}hether persons of relevant practical knowledge and experience would understand that strict compliance with a particular descriptive word or phrase was intended by the patentee to be an essential requirement of the invention.")[1069] both approaches are comparable. Nevertheless, the German law not only determines when equivalents *per se* is excluded, but provides sets the framework for how it must be narrowed under certain conditions.[1070]

The first question in the *Cutting Blade I* decision ("whether the allegedly infringing product solves the problem underlying the invention with modified but objectively equivalent means") resembles the first *Catnic* question, but is slightly different.[1071] It is not asked whether a different means "works in the same way" but whether it solves the problem underlying the invention by means which have the same technical effect.[1072] The latter must be identical; even small discrepancies result in the rejection of equivalents. The decision of whether the variants provide the

1066 BGH, 34 IIC 197, 197 (2003) - Custodiol II.

1067 BGH, 34 IIC 197, 202-203 (2003) – Custodiol II; Meier-Beck, Peter, Aktuelle Fragen der Schutzbereichsbestimmung im deutschen und europäischen Patentrecht, GRUR 2003, 905, 910.

1068 Catnic Components Ltd v Hill & Smith Ltd, [1981] F.S.R. 60 (House of Lords 1980).

1069 Catnic Components Ltd v Hill & Smith Ltd, [[1981] F.S.R. 60, 61.

1070 Meier-Beck, Peter, Aktuelle Fragen der Schutzbereichsbestimmung im deutschen und europäischen Patentrecht, GRUR 2003, 905, 909; there also exist differences from the protocol question; such as that claims are not only considered to be the starting point, but also the decisive basis for determining the extent of protection, see Meier-Beck, Peter, The Scope of Patent Protection - The test for Determining Equivalents, 36 IIC 339, 341(2005); different view Benkard/Scharen, EPÜ, Art. 69, Nos. 72-75, stating that a distinction between essential and non-essential aspects of the claim language is contrary to patent law.

1071 Meier-Beck, Peter, The Scope of Patent Protection - The test for Determining Equivalents, 36 IIC 339, 342 (2005).

1072 Meier-Beck, Peter, The Scope of Patent Protection - The test for Determining Equivalents, 36 IIC 339, 343 (2005); Kirin-Amgen Inc v. Hoechst Marion Roussel, [2005] R.P.C. 9, 2004 WL 2330204, No. 75.

same effects is based on grounds of the claims. A technical effect is only considered to be the same if it describes all the effects that a skilled person understands from the claim to be set forth by every single feature and by the mutual connection of all features of the claim. Technical effects are understood as the results of the technical teaching of the claim.[1073] The first question of *Cutting Blade I* must be read in the light of another decision made by the German Federal Supreme Court. In *Roasting Pots*[1074], the German court stated that the examination of whether a means is objectively equivalent must also be determined in orientation to the patent claim language. The headnote explains that an inquiry is necessary, which considers not only the final result of the problem solution to be equally effective, but also all characteristics that are involved in the problem solution process. Thus, the skilled person must be able to predict each single element of such a process. With regard to numeric measurements, the application of this rule results in that the person skilled in the art must be able to obtain not only equal results by using a modified numeric term, but also exactly the same result as is claimed. [1075]

Finally, the second question of the *Cutting Blade I* decision ("whether the person skilled in the art is able to use his specialist knowledge to identify the modified means as having the same effect") is considered. It simply asks whether the person skilled in the art is able to find modified means that gives rise to the same effects.[1076]

Altogether, the legal treatment of figures and measurements establishes a standard for equivalents, which is significantly stricter than earlier applied approaches. [1077] In earlier decisions, it had been sufficient for a substance patent to cover equally effective variants, provided a person skilled in the art could easily have predicted them to be equally effective as the original protein by reading the patent as a whole.

bb) Transfer of the case law related to figures and measurements to the field of 3-D protein structures inventions

Is the recent German case law concerning the doctrine of equivalents applicable to protein inventions? Some have complained that infringement under equivalents would *per se* be contradictory to the concept of absolute product protection. According to *Benkard/Scharen*, the use of the doctrine of equivalents for the extension of

1073 Meier-Beck, Peter, The Scope of Patent Protection - The test for Determining Equivalents, 36 IIC 339, 343 (2005).

1074 BGH, 33 IIC 349 (2002) – Roasting Pots (Bratgeschirr).

1075 Meier-Beck, Peter, Aktuelle Fragen der Schutzbereichsbestimmung im deutschen und europäischen Patentrecht, GRUR 2003, 905, 908.

1076 BGH, 33 IIC 873, 875 (2002) – Cutting Blade I (Schneidmesser I); Meier-Beck, Peter, Aktuelle Fragen der Schutzbereichsbestimmung im deutschen und europäischen Patentrecht, GRUR 2003, 905, 908; Busse/Keukenschrijver, PatG, § 14, No. 43.

1077 Benkard/Scharen, Patentgesetz, § 14 No. 67. Earlier decisions understood figures and measurements as a mere exemplary determination of the claimed technical teaching, see RGZ 86, 412, 416; RG GRUR 28, 481.

scope of absolute product patents seems impossible. He asserts that abstract, equally effective results can only be achieved by identical substances. Yet, no chemical substance can be equivalent to another chemical substance. [1078] The determination of equivalents at least requires one category in which two means/substances are equally effective. With substances lacking such category, opponents allege that they cannot establish any equivalents.[1079]

These arguments, however, are not persuasive in light of European Directive 98/44/EC, pursuant to which every genetic sequence must indicate its function, e.g., the encoded protein and the effect the protein is providing.[1080] This principle was incorporated into the EPC. Pursuant to Implementing Regulation to the EPC, Rule 43 (former Rule 29), "the industrial application of a sequence or a partial sequence of a gene must be disclosed in the patent application."

Accordingly, protein inventions typically disclose a function. They not only indicate the essential properties, which are responsible for certain functions, but also determine the structural features that result in similar or equal groups of protein domains and active centres. Thus, with such equally effective category being provided, infringement under the doctrine of equivalents is possible.[1081]

But, how are the principles set forth in *Cutting Blade I* related to the initial question of whether a patent can be extended to sequence-dissimilar proteins sharing common folds and effects? As reported above, in addition to the requirement that the modified means must be objectively equivalent (*Cutting Blade*-question No. 1) and predictable for persons skilled in the art (*Cutting Blade*-question No. 2), the different embodiment that is accomplished with modified means must be equivalent to the solution in question (*Cutting Blade*-question No. 3).[1082] With regard to the last, the proteins' underlying biological function is considered a technical effect that is accomplished by an equivalent embodiment - the same folding type. This folding type must be covered by the semantic meaning of the original patent. Hence, the original patent must indicate the characteristic properties, such as core folding residues that are responsible for the cause of function. A skilled person must then be able to rely upon this information and to classify the folding type to which a claimed protein belongs. Due to the provided information, the skilled person must be able to understand which of the disclosed properties are responsible for the biological function. Folding types bearing same effects due to the same binding or inhibitor activities are

1078 Benkard/Scharen, Patentgesetz, § 14, No. 55; also, Lederer, Franz, Equivalents of Chemical Product Patents, 3 IIC 275, 275 (1999).

1079 Hirsch, Fritjoff/Hansen, Bernd, Der Schutz von Chemie-Erfindungen, Weinheim, New York, Basel, Camebridge, Tokyo 1995, 293.

1080 Directive 98/44/EC states: "Whereas a mere DNA sequence without indication of a function does not contain any technical information and is therefore not a patentable invention."

1081 BGH, GRUR 1984, 425 – Bierklärmittel; Lederer, Franz, Equivalents of Chemical Product Patents, 30 IIC 275 (1999) or Meyer-Dulheuer, K.-H., Der Schutzbereich von auf Nucleotid- oder Aminosäurensequenzen gerichteten biotechnologischen Patenten, GRUR 2000, 179, 182.

1082 Chapter 4 C IV 3 b) aa).

considered equivalents. If different residues or other decisive folding aspects are responsible for the same/similar effects or functions, they lack a relationship to the original protein and thus do not suffice. In sum, an analysis based on the *Cutting Blade* inquiry demands a thorough examination that resembles the standards required by the 'function-way-result' method. Both patent law systems are in this context comparable.

Does the German approach allow that patent claims extend to unforeseeable technologies under the doctrine of equivalents? Are as yet unidentified tertiary structures bearing the same functions/effects as the earlier patented protein encompassed by the original patent claim? This question had been already asked with regard to the discussed-above U.S. patent law system. Thus, it is necessary to ask whether patent claims can be interpreted broadly enough to encompass new technologies achieving same effects. Here, much depends on the second *Cutting Blade* question, asking whether a skilled person is able to identify the modified means having the same effects. As set forth in the introduction, the German Patent law system determines equivalents at the time of priority.[1083] It follows that new technologies, i.e., yet unknown means, would not be covered by earlier issued patents, since a person skilled in the art at the time of priority is not able to foresee later-arising ways to achieve same functions. The German law, however, allows that the skilled person (who was able to identify a modified means at the time of priority) relies on his earlier awareness if the identified means in the future is replaced by a new technology that was still unknown at the time of priority.[1084] Hence, claims are interpreted sufficiently broadly to encompass new techniques if the newly developed means replace the earlier means that had been predictable for the person skilled in the art. Insofar the German patent law that in principle determines equivalency at the time of priority comes to the same conclusion as the U.S. law that evaluates equivalency at the time of infringement. A more restrictive approach, however, has been employed in another European country. In the already mentioned *Amgen v. TKT* case, the English House of Lords denied equivalents with regard to *TKT's* new method for manufacturing DNA by gene activation.[1085] *Amgen* used an exogenous DNA sequence coding for ''Epo'' which has been introduced into an host cell, wheras *TKT* was able to achieve the same results by an endogenous DNA sequence coding for ''Epo'' in a human cell into which an exogenous control sequence has been inserted.[1086] Amgen argued that its claims must be construed in terms sufficiently general to include me-

1083 See Chapter 4 B II b); Benkard/Scharen, GPA, § 14 , No. 111.

1084 Benkard/Scharen, GPA, § 14 , No. 113, 117; Kraßer, Rudolf, Patentrecht: ein Lehr- und Handbuch zum deutschen Patent- und Gebrauchsmusterrecht, europäischen und internationalen Patentrecht, 5. Aufl., München 2004, 753; Falck, Kurt von, Zur Äquivalenzprüfung bei im Prioritätszeitpunk noch unbekannten Ersatzmitteln, GRUR 2001, 905, 907; according to Tilmann, Winfried/Dagg, Nicola, EU-Patentrechtsharmonisierung I: Schutzumfang, 2000, 459, 465, determination of equivalents is made at the time of infringement.

1085 Kirin-Amgen Inc. and others v Hoechst Marion Roussel Ltd and others, [2005] R.P.C. 9 (House of Lords 2004).

1086 For the detailed factual background see Chapter 3 A II 3 b) a).

thods unknown at the priority date to cover new technologies for achieving same results. Thus, the claim should be read as including any DNA sequence, whether exogenous or endogenous, which expresses 'Epo' in consequence of the application to the cell of any form of DNA recombinant technology.[1087] Lord Hoffman, for the House of Lords, denied such an expansion of the words of the claims under the doctrine of equivalents. The judge emphasized that "there is no difficulty in principle about construing general terms to include embodiments which were unknown at the time the [patent] was written". However, a claim must be properly construed "in a way which was sufficiently general to include the new technology".[1088] In this respect, Lord Hoffmann explained:

> "'Purposive construction' does not mean that one is extending or going beyond the definition of the technical matter for which the patentee seeks protection in the claims. The question is always what the person skilled in the art would have understood the patentee to be using the language of the claim to mean... There will be occasions upon which it will be obvious to the skilled man that the patentee must in some respect have departed from conventional use of language or included in his description of the invention some element which he did not mean to be essential. But one would not expect that to happen very often."[1089]

Thus, the House of Lords precluded any protection of equivalents beyond the "purposive interpretation" of a patented invention. Nevertheless, the rationale demonstrates that it is not *per se* impossible to claim yet unknown technologies. In the dispute, Amgen would have been aware that recombinant technologies were developing rapidly and that new approaches had been achieved in bacterial and yeast cells and that their use in mammalian cells was regarded a desired goal. Thus, it would have been able to rely upon equivalents if it had drafted claims broadly enough to indicate a person skilled in the art that new developments of manufacturing recombinant ''Epo'' were included.[1090]

Notwithstanding this general possibility of claiming new technologies, the U.K. formulation differs sharply from the U.S. approach. Here, the skilled person can rely upon the knowledge that exists at the time of infringement.[1091] Consequently, he is allowed to consider developments that were yet unknown in the time of priority. The U.S. concept is thus significantly broader than the British one. Further developments must demonstrate whether other European countries, such as Germany, will follow the British example. In the meantime, a high level of uncertainty surrounds the application of the doctrine of equivalents for new techniques that achieve the same results as earlier claimed inventions. With regard to the initial question of the treatment of sequence-dissimilar proteins achieving the same effects as earlier claimed

1087 Kirin-Amgen Inc. and others v Hoechst Marion Roussel Ltd and others [2005] RPC 9, No. 2.
1088 Kirin-Amgen Inc. and others v Hoechst Marion Roussel Ltd and others [2005] RPC 9, No. 80
1089 Kirin-Amgen Inc. and others v Hoechst Marion Roussel Ltd and others [2005] RPC 9, No. 34.
1090 Kirin-Amgen Inc. and others v Hoechst Marion Roussel Ltd and others [2005] RPC 9, No. 78.
1091 Warner-Jenkinson, 520 U.S. 17, 37.

proteins, it is thus still uncertain what courts will demand that patentees include in the patent involving the original protein.

c) Conclusions

Under the U.S. patent law system, the 'function-way-result' method is considered an adequate means for determining equivalents. A sequence-dissimilar protein can be considered to satisfy the 'way'-prong of this 'triple-identity' – inquiry, while a protein bearing a different fold must be considered to accomplish the function a different 'way'. It is further appropriate to require patentees to generate precise structural information, because the state of the art in protein science has significantly improved due to advanced functional proteomic analysis. In particular, methods capable of accomplishing in-depth protein structure determination have been developed. An expansion of claim coverage to as yet unidentified sequence-dissimilar proteins sharing common folding properties and effects is not limited. Prosecution history estoppel does not bar patentees. The flexible bar rule allows inventors to claim equivalents for elements that have been unforeseeable at the time of the amendment. Furthermore, generic disclosure in the patent specification, such as the indication of 3-D folding characteristics does not automatically result in a dedication of all members of the particular genus to the public. It is, however, necessary to disclose the genus in a manner that would suggest the disclaimer of alternative, as yet unknown species.

Unlike the U.S. approach, German patent law does not address the question of equivalents on a case-by-case basis, although the established and generalized principles are derived from case law related to figures and measurements. In sum, these principles require a theoretical analysis under Art. 69 EPC to determine whether the use of protein variants has the same effect as the patented technical teaching. The decisive element of the '*Cutting Blade*-questions' discussed above is the presence of a technical effect that must be identical *and* predictable for a person skilled in the art.[1092] The folding type is considered the modified means that is responsible for the biological effect, or, in other words, the proteins' function. A patentee must therefore include the properties responsible for the conduct of function, thus binding or inhibiting residues. A skilled person must rely upon this information and be able to predict which proteins belong to the same folding type due to similar properties that cause like/similar folding types. The examination required for the reasons set forth above significantly resembles the function-way-result approach conducted under the U.S. patent law system.

Although the German patent law system determines equivalency at the time of priority, it allows claims to be equivalently expanded to later-arising technologies,

1092 Meier-Beck, Peter, The Scope of Patent Protection - The test for Determining Equivalents, 36 IIC 339, 342 (2005); Kirin-Amgen Inc v. Hoechst Marion Roussel, [2005] R.P.C. 9, 2004 WL 2330204, Section 75.

such as yet unidentified sequence-dissimilar proteins bearing the same functions. A person skilled in the art must be able to replace the means that had been predictable at the priority date by the later-developed new technology. Like in the U.S., the decision upon equivalents is consequently made in light of later disclosed knowledge. Despite of the broad German approach, the U.K. in the recent TKT decision employs a more restrictive method of determining equivalents. The U.K. formulation precludes any protection of equivalents that is beyond the "purposive interpretation". If this approach is followed by other European countries, the possibility of expanding claims by reliance upon equivalency is significantly narrowed.

In sum, the above analysis shows that the doctrine of equivalents might clearly be available in some cases related to proteins that share common folding types.[1093] Nevertheless, difficulties do arise with regard to the prediction of whether equivalents can be established. In the U.S., the function-way-result method requires patentees to include substantial knowledge regarding the 3-D protein structure into the patents. If this information is included in the claim language, narrowing amendments during the application procedure might be necessary. Consequently, prosecution history estoppel might bar inventors from reliance upon equivalents subject to already-known proteins. If the information related to 3-D structure is indicated in the patent specification rather than in the claims, patentees risk dedication of their knowledge to the public. Then, a reliance upon equivalents is barred by the public-dedication rule, unless the 3-D structural information for specific proteins, such as unidentified ones, is explicitly disclaimed.

In Germany, the necessary theoretical inquiry derived from the case law related to figures and measurements requires the presence of a technical effect. A person skilled in the art must then rely upon a step-by-step description in the claim language and evaluate whether the potentially infringed embodiment is entirely present in the competitive product. The equivalent determination of a tertiary folding type, however, introduces a significant level of complexity which may overwhelms courts and patent examiners. Consequently, it is difficult to predict to which extend the determination of equivalents regarding protein folds is already understood by the person skilled in the art.[1094] Furthermore, the U.K. formulation of equivalents, i.e., the requirement to draft claims sufficiently general that persons skilled in the art understand the inclusion of a new technology challenges inventors to foresee what will be invented in the future. From this restrictive perspective, and the overall uncertainty

1093 Holman, Christopher M., Protein similarity score: a simplified version of the blast score as a superior alternative to percent identity for claiming genuses of related protein sequences, 21 Santa Clara Computer & High Tech. L.J. 2004, 55, 61.

1094 Bergen-Babinecz, Katja/Hinrichs, Nikolaus/Jung, Roland/Kolb, Georg, Zum Schutzbereich von US-Patenten: Festo und eine deutsche Sicht, GRURInt. 2003, 487, 487 citing Judge Michel from the CAFC who emphasizes the high level of uncertainty surrounding the doctrine of equivalents.

surrounding this area of the law, the inventor should, to the extent possible, seek broad literal coverage rather then rely upon the doctrine of equivalents.[1095]

V. U.S. Patent No. 5,835,382 "Small Molecule Mimetics of Erythropoietin"[1096]: A characteristic proteomic patent

A number of cases involving the filing of patents involving protein crystal structure determination have been described. Furthermore, the case study illustrated further claims related to proteomic research, among them claims to 3-D structural data directed towards the use of structural data in rational drug design. To substantiate the results of these concrete claims, it is useful to consider another patent. Specifically, the legal treatment of a patent directed to the screening of erythropoietin (''Epo'') mimetics will be reviewed, since it encompasses a number of characteristics typical of proteomic inventions.[1097] In particular, it demonstrates an indirect way to claim a protein defined by its folding type and may also involve screened sequence-dissimilar proteins consisting of the same folding type as the ''Epo'' molecule. The invention involves a computer-assisted method for identifying molecules that are able to bind to the ''Epo'' receptor. Due to their structural similarity these ''Epo'' 'mimetics'[1098] act in the same fashion as ''Epo''. In particular, they are capable of binding to the ''Epo'' receptor. Since they display the response usually found in ''Epo'', the identified compounds emulate the important functions that are otherwise performed by the ''Epo'' molecule, acting as agonists of the ''Epo'' receptor. The claimed method is conducted on grounds of precise structural information obtained from x-ray crystallographic methods of the extracellular domain of ''Epo'' receptor linked to a binding peptide (which acts as an ''Epo'' mimetic). This crystallographic data enables the identification of atoms in the peptide mimetic that are significant

1095 Holman, Christopher M., Protein similarity score: a simplified version of the blast score as a superior alternative to percent identity for claiming genuses of related protein sequences, Holman, Christopher M., Protein similarity score: a simplified version of the blast score as a superior alternative to percent identity for claimng genuses of related protein sequences, 21 Santa Clara Computer & High Tech. L.J. 2004, 55, 61 who recommends not relying on the doctrine in order to expand the claim coverage on protein variants.

1096 Wilson; Ian A./Livnah; Oded/Stura; Enrico A./Johnson; Dana L./Jolliffe; Linda K., Small molecule mimetics of erythropoietin, La Jolla 1998.

1097 Wilson; Ian A./Livnah; Oded/Stura; Enrico A./Johnson; Dana L./Jolliffe; Linda K., Small molecule mimetics of erythropoietin, La Jolla 1998, see also Meyers, T. C./Turano, T. A./Greenhalgh, D. A./Waller, P. R., Patent protection for protein structures and databases, 7 Suppl Nature Structural Biology 2000, 950, 951.

1098 The term "Mimetics" refers to selected chemical structures similar to the three-dimensional structure of the subset of atoms of the the 'EPO' peptide, see Meyers, T. C./Turano, T. A./Greenhalgh, D. A./Waller, P. R., Patent protection for protein structures and databases, 7 Suppl Nature Structural Biology 2000, 950, 951.

for ‘‘Epo’’ receptor binding. This data includes a 3-D array of the important contact atoms.[1099]

The written description reveals the tertiary structure of the ‘‘Epo’’ receptor and discloses the binding properties of potential ‘‘Epo’’ mimetics. It determines that other molecules including a portion in which the atoms have a 3-D structure similar to some or all of the ‘‘Epo’’ contact atoms are likely to be capable of acting as an ‘‘Epo’’ mimetic. The description further discloses that a peptide considerably smaller than the natural ‘‘Epo’’ can act as an agonist and induce an adequate biological response. Thereby, it is assumed that the binding peptide forms a substantially smaller contact interface than the natural ‘‘Epo’’ with the receptor. The description also concludes that the identification of the most crucial residues and functional key interactions provides a practical target for drug design.[1100]

To get a better sense of what is exactly claimed, it is useful to reproduce excerpts of the actual specification. It reads as follows:

1. A computer-assisted method for identifying potential mimetics of erythropoietin, using a programmed computer comprising a processor, a data storage system, an input device, and an output device, comprising the steps of:
   (a) to ... (d)
2. A computer-assisted method for identifying potential mimetics of erythropoietin, using a programmed computer comprising a processor, a data storage system, an input device, and an output device, comprising the steps of:
   (a) to ... (c)
3. A compound having a chemical structure selected using the method of claim 1, said compound being an ‘Epo’ mimetic.
4. ...[1101]
5. The compound of claim 3 wherein said compound is a peptide.
6. The compound of claim 5 wherein said peptide has 15 of fewer amino acids.[1102]

The patent includes various aspects that are remarkable in light of the discussion above. With regard to the demonstrated invention involving a natural ‘‘Epo’’ product, it must be distinguished, because it is not directed to the purification of natural ‘‘Epo’’, but rather to its replacement through a different protein. The underlying motivation of the inventors, however, might be similar; both methods may enable drug design independent of recombinantly obtained ‘‘Epo’’ molecules. The former method obtains the ‘‘Epo’’ molecule from urine, plasma or other substances; the latter

1099 Wilson; Ian A./Livnah; Oded/Stura; Enrico A./Johnson; Dana L./Jolliffe; Linda K., Small molecule mimetics of erythropoietin, La Jolla 1998.

1100 Wilson; Ian A./Livnah; Oded/Stura; Enrico A./Johnson; Dana L./Jolliffe; Linda K., Small molecule mimetics of erythropoietin, La Jolla 1998.

1101 Claim 4 referred to non-peptide molecules that are not subject of this analysis.

1102 Wilson; Ian A./Livnah; Oded/Stura; Enrico A./Johnson; Dana L./Jolliffe; Linda K., Small molecule mimetics of erythropoietin, La Jolla 1998.

is directed to the identification of 'Epo' mimetics that equally perform the natural ''Epo'' functions.[1103]

As to the question of dependency, it is relevant that the computerized data related to the ''Epo'' receptor has been obtained on grounds of recombinant technologies and associated crystallizing methods not encoding ''Epo'' itself, but rather the membrane receptor protein to which ''Epo'' binds. High relevance is established with regard to the question of whether dissimilar proteins bearing structural similarities and function infringe earlier issued patents. From the perspective of inventors holding patents to the original ''Epo'', the claimed ''Epo'' mimetics might represent a case of sequence-dissimilar proteins having equal/similar folding features and functions as the native ''Epo''. It is also worth noting that the question of 'reach-through claiming' is not raised. Potentially screened ''Epo'' mimetics are precisely defined by size and shape. The patent description thus provides sufficient information for matching the enablement requirement.

In terms of scope of protection issues, it is clear that anyone who uses the coordinates to identify structures similar to the specified peptide may be an infringer and consequently may be liable for damages and prohibited from using this method to find ''Epo'' mimetics. As for patent dependency and infringement of other patents, the following rules can be established. First, the computerized method stimulates the ''Epo'' receptor rather than the ''Epo'' molecule itself. Hence, no patent dependency exists with regard to inventions involving the natural or the recombinantly obtained ''Epo''. Second, the structural data referring to the ''Epo'' receptor relies on recombinantly produced molecules and crystallographic analysis. Therefore, patent dependency with regard to potential patents covering these crystallizations methods is established. Additionally, patents involving the recombinant production of ''Epo'' receptors are infringed. Patents for recombinantly obtained ''Epo'' molecules are not infringed unless the patent owner includes structural knowledge as to the crucial binding residues and core interaction features, i.e., atoms. In this event, the patent is extended to the ''Epo'' mimetic molecule determined by this information pursuant to the doctrine of equivalents.

The patent demonstrates the great significance of the above conducted discussion on infringement through the use of sequence-dissimilar proteins or other non-patented molecules. In order to 'invent around' existing patents, inventors search for proteins that are not yet patented but able to perform similar biological functions. Attempts to find alternatives for patented compound occur also in the field of prion research. For example, U.S. Patent 5,773,572, entitled "Fragments of prion proteins", concerns synthetic polypeptides that emulate the 3-D structures of proteins involved in mental prion disorders.[1104]

1103 Wilson; Ian A./Livnah; Oded/Stura; Enrico A./Johnson; Dana L./Jolliffe; Linda K., Small molecule mimetics of erythropoietin, La Jolla 1998

1104 U.S. Patent 5,773,572 "Fragments of prion proteins" by Fishleigh, Robert Vincent/Robson, Barry/Mee, Roger Paul, Macclesfield 1998.

VI. Use of selective 3-D protein structure parts (Selection inventions)

1. Relationship to patents covering the entire protein

With regard to a selection invention, it is primarily the dependency on the patent that covers the entire protein that has to be considered. Hence, the patent to the genetic sequence is only involved if the entire protein is part of a patented recombinant process. A potential claim to a selective part of a protein has already been analyzed in the case study above,[1105] but shall be introduced again, reading as follows:

> An isolated and purified polypeptide consisting of a portion of protein P starting at one of amino acids 214 to 218 and ending at one of amino acids 394 to 401 of protein P as set forth in SEQ ID NO: 1.[1106]

As introduced above, "selection inventions" claim a narrow range within a broad scope disclosed by the prior art. [1107]Besides determining the "obviousness" of a claim to a selective field of a broader invention, the question of patent dependency is a decisive element of selection inventions. For classification of the problem, the same principles are applied as those used for the treatment of "improvement inventions". Developments of improved versions of drugs are not necessarily directed to a selective part of the earlier invention, but can also cover additional aspects or the broadening of the earlier version. Generally the term "improvement" is used as an "umbrella term" and also includes the cases in which one "invents around" an existing invention, e.g. attempts to advance the existing technique by using different compounds or facilities without touching the scope of the existing patent.[1108] With the high standard of the "obviousness" factor developed in the field of "selection inventions", the inventive step requirement, however, always includes an improvement over the earlier invention, and the prior art, respectively. Thus, even though not all improvements of a drug produce selectivity, each selective invention can be considered as improvement. The same protein can be used in an improved manner due to the disclosure made with regard to the binding pockets. Generally, patent law does not vest in the original patent holder any right to improvements or derivative inventions and new patents can be granted for the selective part if all other requirements are met. In most cases, the selective patent is "blocked" by the original patent holder, meaning that the selection invention cannot be used without a license from the original patent holder whose technology has been incorporated into the improved

1105 Chapter 3 B II 2 a).

1106 European Patent Office, Japan Patent Office, United States Patent and Trademark Office, Trilateral Project WM4, Comparative Studies in New Technologies (Biotechnology, Business Methods, etc.), Report on Comparative Study on Protein 3-Dimensional (3-D) Structure Related Claims, Vienna 2002, 9.

1107 Chapter 3 B II 2 d).

1108 Dow, Kenneth J./Quigley, Traci Dreher, Improvements for handling improvement clauses in IP licenses: an analytical framework, 20 Santa Clara Computer & High Tech. L.J. 2004, 577, 580-581.

entity.[1109] Likewise, the original patent holder is blocked from using the selection invention. Hence, at least one of the patent owners needs a license from the other in order to use the invention. With the threat of mutual patent blocking, it might be advisable for both patent holders to determine the details of patent use by negotiated agreement.[1110]

As for a selection invention, concerns and objectives of both the owner of the broader, and the owner of the narrow, patent are relatively clear. Typically, the patentee of a selection invention involving a protein domain is interested in producing the protein in a recombinant fashion. Even though his invention may have been developed without the use of a recombinant process, e.g., by determining the binding pockets through protein crystallization or *in silico* screening methods, in most cases a large amount of highly purified proteins is required in order to exercise his invention. Thus, he needs to license the use of a recombinant process. If the owner of the recombinant process is interested in using the improvements of the selective parts, cross licensing can be considered. The particular negotiation and defining of improvement clauses is generally a difficult task.[1111] In the case of a selection invention, however, it is still relatively easy. As the improvement must consist of the properties of a selective part of the earlier invention, the improvement clause has to cover all cases in which the use of the improved product was based on selective properties or the earlier patented product.

In the cases in which the improvement is not related to any selective part, but instead to aspects such as other compounds used or protein analogs or variants being developed, licensing clauses might create considerable difficulties. The concerns and objectives of both parties may be quite divergent. For example, a licensor who developed a specific product or process and plans to continue the advancement of this technology may not wish his improvement to automatically be subsumed within his original agreement with the licensee. On the other hand, the licensee might be concerned about the restrictions that are conveyed by the improvement clause, such as typically used obligations, regarding the further exploitation of the improvements. The definition of the term "improvements" is thus an essential element and existing case law still leaves many questions unanswered. In *Deering Milliken*, the court held that a clear definition of what is considered as an improvement requires "clear, deliberate, and appropriate language".[1112]

1109 Dow, Kenneth J./Quigley, Traci Dreher, Improvements for handling improvement clauses in IP licenses: an analytical framework, 20 Santa Clara Computer & High Tech. L.J. 2004, 577, 581.

1110 Dow, Kenneth J./Quigley, Traci Dreher, Improvements for handling improvement clauses in IP licenses: an analytical framework, 20 Santa Clara Computer & High Tech. L.J. 2004, 577, 581.

1111 Brunsvold Brian G./O'Reilley, Dennis P., Drafting Patent License Agreements, 5th ed. Washington D.C. 2004, 99.

1112 Deering-Milliken Research Corp. v. Leesona Corp., 201 F. Supp. 776 (E.D.N.Y. 1962), aff'd 315 F.2d 475 (2d Cir. 1963).

2. The Amgen case

The importance of improvement clauses and their interpretation is illustrated by the Amgen case.[1113] Amgen, a newly founded biotechnology firm, owned two promising drugs, Epogen and Neupogen. Faced with financial problems, the firm did not have sufficient funding to develop the two pharmaceuticals. Due to this pressure, Amgen created the following deal with Ortho Pharmaceuticals. In exchange for a much needed credit of $ 10 million dollars, Amgen conveyed Ortho exclusive worldwide rights to sell ''Epo'' while retaining its own rights to sell ''Epo'' for the kidney dialysis market in the U.S. The deal proved to be a lifesaver for Amgen, but also made the company lose more than two-thirds of the market for its Epogen drug.[1114] A couple of years later, Amgen developed a new-improved version of "Epo", a hyperglycosylated analog of ''Epo'' known as NESP. Amgen alleged the drug to have the advantage of a three-fold longer half-life than the original ''Epo'', resulting in less frequent dosing.[1115] In order to gain access to the lucrative worldwide non-dialysis market that was estimated to amount to at least 1.35 billion in 1998, Amgen argued that NESP was not covered by the 1985 license agreement with Ortho. Ortho countered that NESP was an improvement covered by the agreement to which it had exclusive rights outside the dialysis market. The arbitration panel, which took over the case, finally decided that Amgen had exclusive rights to NESP and that the new analog could not be considered as an improvement covered by the elaborated license. The ruling not only resulted in giving Amgen access to the lucrative market for ''Epo'', but also raised Amgen's shareholder value more than 23%.[1116] The case helped Amgen to develop into one of the world's largest biotechnology firms.[1117]

3. Applicable law

With regard to selection inventions, little difference exists between the U.S. and Europe. As for the European system, the principles applying to a selection invention have already been described above.[1118] Novelty presupposes that the selected subfield is narrow, that it contains sufficient distance to the known range illustrated by

1113 A detailed description of the case can be found in Fürst, Ingeborg, Amgen's NESP victory cuts out Johnson & Johnson, 17 Nature Biotechnology 1999, 124, 124; see also Straus, Joseph, Genpatente: rechtliche, ethische, wissenschafts- und entwicklungspolitische Fragen, Basel, Frankfurt/Main 1997, 50.

1114 Dow, Kenneth J. /Quigley, Traci Dreher, Improvements for handling improvement clauses in IP licenses: an analytical framework, 20 Santa Clara Computer & High Tech. L.J. 2004, 577, 578.

1115 Dow, Kenneth J. /Quigley, Traci Dreher, Improvements for handling improvement clauses in IP licenses: an analytical framework, 20 Santa Clara Computer & High Tech. L.J. 2004, 577, 578.

1116 Fürst, Ingeborg, Amgen's NESP victory cuts out Johnson & Johnson, 17 Nature Biotechnology 1999, 124, 124.

1117 See Amgens' home page available at http://www.amgen.com/, last checked on January 21, 2008.

1118 Chapter 3 B II 2 d).

working examples, that it is not randomly selected, but is the result of a more tightly-focused selection and that it provides not only an embodiment of the prior art description, but also a further invention.[1119] Nonobviousness/inventive step require an outstanding effect, property, or use when compared with compounds in the known generic invention.[1120] Under both systems, European and the U.S., a patent involving a selection invention always depends on earlier issued patents covering the entire subject. Consequently, the use of a patent to a selective protein part automatically infringes the patent directed to the entire protein.[1121]

With regard to general improvement patents, the crucial question is whether the skilled person was able to predict the improved technology. This is questionable, if the considerations leading the skilled person are based on inventive activity.[1122] One receives a patent based on inventive activity, provided that all further patentability requirements are fulfilled. The scope of protection of earlier issued patents might then equivalently expand to the new technology and create dependency. In this event, the later-issued patent will depend on the earlier issued patent. The two German Federal Supreme Court's decisions *Fixing Device II*[1123] and *Segmentation Device for Trees*[1124] have provided rulings on the subject. The first impression is that both rulings appear contradictory. In *Fixing Device II*, the court stated that:

> [t]he scope of protection of a patent can also include such embodiments that make *use of the protected teaching* while also implementing *an inventive further realization;* it is then a dependent invention.[1125]

Headnote No.1 of the decision *Segmentation Device for Trees* by contrast determines that:

> "The extent of protection of a patent according to Sec. 14 of the Patent Act 1981 is in any event no greater than the extent of protection of a patent according to the previously applicable law. It does not comprise *equivalent derivations based on an inventive step."*[1126]

Hence, any inventive *further realization* that uses the technical teaching of the patented invention results in an infringing act, but an *equivalent derivation based on an inventive step* does not. Accordingly, it is of the essence as to whether the contested embodiment uses and further develops the patented invention or whether it is

1119 Blumer, Fritz, Formulierung und Änderung der Patentansprüche im europäischen Patentrecht, München 1998, 345.
1120 Blumer, Fritz, Formulierung und Änderung der Patentansprüche im europäischen Patentrecht, München 1998, 358.
1121 Meyers, T. C./Turano, T. A./Greenhalgh, D. A./Waller, P. R., Patent protection for protein structures and databases, 7 Suppl Nature Structural Biology 2000, 950, 951. The previously issued patent to the entire molecule may thus also be referred to as the dominant patent.
1122 Kraßer, Rudolf, Äquivalenz und Abhängigkeit im Patentrecht, Tübingen 1998, 516, 527.
1123 BGH, 23 IIC 111(1992) - Fixing Device II (Befestigungsvorrichtung II).
1124 BGH, 26 IIC 261 (1995) - Segmentation Device for Trees (Zerlegevorrichtung für Baumstämme).
1125 BGH, 23 IIC 111 (1992) - Fixing Device II (Befestigungsvorrichtung II).
1126 BGH, 26 IIC 261, 261 (1995) - Segmentation Device for Trees (Zerlegevorrichtung für Baumstämme).

inventively derived. The invention involved in *Fixing Device II*, by contrast, only involved a further development, since the general concept of the invention was used only in a slightly different way.[1127] In contrast, *Segmentation Device for Trees* dealt with the question of equivalent derivation based on an inventive step.[1128] The court emphasized the importance of the principle of legal certainty which *de facto* results in a limitation of the scope of protection. Further developments that have been made on grounds of inventive activity of third parties should not be interpreted as having been encompassed by the original claim language. The patent owner does not profit from the work done by others. [1129] In this respect, the court referred to principles established by the German Federal Supreme Court, namely, that no motivation exists for society to grant protection to an inventor if he has not provided any specific and clearly determined mental activity.[1130] Hence, neither the German Patent Act nor constitutional principles can justify an extension of the scope of protection to an equivalent derivate based on an inventive step that goes further than the patented invention.

None of these decisions, however, specified how the inventive activity should precisely be determined. This missing explanation caused wide-ranging discussions in the literature. General interpretations concluded that it is not contradictory to assume the contested embodiment to be inventive and equivalent at the same time. With the patenting of the contested embodiment and the infringement of the patent not ruling each other out, the mere fact that a patent has been granted for the contested embodiment does not by itself disprove equivalents.[1131]

The decision *Snow Removal Blade*[1132]*,* which dealt with the different embodiments of a snow-crawler bar, brought more clarity to this question. Here, the court distinguished between two different kinds of properties an invention may contain: substituted properties and properties that improve an earlier invention through the addition of further elements. In the event that the substituted property exclusively establishes inventiveness, equivalents must be denied, since a person skilled in the art would not have been able to predict the equal effectiveness.[1133] This rule does not apply in the event that an invention is improved though the addition of further elements/characteristics. In such a case, the principles developed in *Fixing Device II*

1127 BGH 23 IIC 111(1992) - Fixing Device II (Befestigungsvorrichtung II).
1128 BGH, 26 IIC 261, 266 (1995) - Segmentation Device for Trees (Zerlegevorrichtung für Baumstämme).
1129 BGH, 26 IIC 261, 266 (1995) - Segmentation Device for Trees (Zerlegevorrichtung für Baumstämme).
1130 BGH, 26 IIC 261, 267 (1995) - Zerlegevorrichtung für Baumstämme (Segementation Device For Trees).
1131 Meier-Beck, Peter, The Latest Issues in German Patent Infringment Proceedings, 32 IIC 505, 516 (2001).
1132 BGH, 33 IIC 525 (2002) – Snow Removal Blade (Räumschild).
1133 BGH, 33 IIC 525, 531 (2002) – Snow Removal Blade (Räumschild).

continue to be applicable, which results in the conclusion that the contested embodiment falls within the equivalent scope of the earlier granted patent.[1134]

The questions of equivalency and improvement exist under U.S. law as well.[1135] In *Varco L. P. v. Pason,*[1136] the question was whether Varco's claim to an automatic drilling system covered the electronic drilling system later developed by Pason.[1137] Varco alleged that "it first developed an automatic drilling system that uses multiple parameters to regulate the release of the drill string", which is why its patent also covered the electronic system operated by Pason.[1138] The Federal Circuit found the interpretation of claims by the district court, which had denied infringement, to be "unduly restrictive."[1139] The court determined that "because this case seems to present an instance of after-arising technology (e.g., improvements on prior innovations), the district court may find it appropriate to consider infringement under the doctrine of equivalents." [1140]

As under German law, a distinction between improvements that add to the initial patent claim elements and those that substitute for those elements must be made.[1141] Only the latter raises the above discussed problem as to whether equivalency can be found if an ordinary person skilled in the art involves inventive activity in his assumptions. The earlier described *Warner-Jenkinson* decision avoids the question by clearly establishing equivalency as of the date of infringement.[1142] If equivalency is determined at the time of infringement, the inquiry is made in light of later (post-

1134 BGH, 33 IIC 525, 532 (2002) – Snow Removal Blade (Räumschild); Allekotte, Bernd, Räumschild - Neuschnee in der Diskussion über Patentverletzung und efinderische Tätigkeit, GRUR 2002, 472, 475.

1135 Varco L. P. v. Pason, 436 F.3d 1368 (Fed. Cir. 2006), citing the following additional cases: Am. Hosp. Supply Corp. v. Travenol Labs., Inc., 745 F.2d 1, 9 (Fed. Cir. 1984) ("An appropriate range of equivalents may extend to post-invention advances in the art in an appropriate case."); Hughes Aircraft Co. v. United States, 86 F.3d 1566, 1584 (Fed. Cir. 1996), remanded, 520 U.S. 1183, 117 S.Ct. 1466, 137 L.Ed.2d 680 (1997), aff'd, 140 F.3d 1470, reh'g denied, 148 F.3d 1384 (Fed. Cir. 1998), cert. denied, 525 U.S. 1177, 119 S.Ct. 1112, 143 L.Ed.2d 108 (1999) (stating that an inventor is not required to predict all future developments that enable the practice of his invention); SuperGuide Corp. v. DirecTV Enter., Inc., 358 F.3d 870, 880 (Fed.Cir.2004) (quoting SRI Int'l v. Matsushita Elec. Corp. of Am., 775 F.2d 1107, 1121 (Fed. Cir. 1985) (en banc)) ("The law 'does not require that an applicant describe in his specification every conceivable and possible future embodiment of his invention.' "); Smithkline Beecham Corp. v. Excel Pharm., Inc., 356 F.3d 1357, 1364 (Fed. Cir. 2004) (stating that the "quintessential example of an enforceable equivalent" is "after-arising" technology); Glaxo Wellcome, Inc. v. Impax Lab. Inc., 356 F.3d 1348, 1354 (Fed. Cir. 2004) (also concluding that the "quintessential example of an enforceable equivalent" is after-arising technology).

1136 Varco L. P. v. Pason, 436 F.3d 1368 (Fed. Cir. 2006).

1137 Varco L. P. v. Pason, 436 F.3d 1368, 1372.

1138 Varco L. P. v. Pason, 436 F.3d 1368, 1370.

1139 Varco L. P. v. Pason, 436 F.3d 1368, 1376.

1140 Varco L. P. v. Pason, 436 F.3d 1368, 1376.

1141 Sarnoff, Joshua, The Doctrine of Equivalents and Claiming the Future after Festo, 14 The Federal Circuit Bar Journal 2004, 403, 410.

1142 Warner-Jenkinson, 520 U.S. 17, 37.

issuance) knowledge.[1143] Thus, the improvement may be a non-obvious improvement at its time of filing, and yet equivalent in light of later arising knowledge. Later arising knowledge might also cause obviousness of the improvement.

VI. Use of compounds identified through 3-D protein structure screening methods

The final question to be analyzed is whether the use of compounds obtained through an *in-silico* screening process infringes the patent that was granted to the screening process itself. As a first step, a recent case related to compounds that have been identified by a patented method and later been imported into the country where the existing patent was originated will be presented. Then, several approaches to the protection of identified compound will be examined.

1. Protection as product of patentable process

Infringement is constituted if identified compounds can be classified as products of a patented process.[1144] Under Art. 64 paragraph 2 EPC and § 9 paragraph 2 No. 3 GPA, a patent to a patented process "shall extend to the product directly obtained by such process." German and other European courts distinguish between patents directed to manufacturing processes or working processes.[1145] Manufacturing processes aim to make a physical product, and the patent to the process extends to such a product. In contrast, a working process does not result in a product, but is typically conducted for the purpose of achieving an abstract result of an action ("abstrakter Handlungserfolg").[1146] A product which is obtained directly from a patented process is the product with which the process ends.[1147] A compound can still be considered

1143 Sarnoff, Joshua, The Doctrine of Equivalents and Claiming the Future after Festo, 14 The Federal Circuit Bar Journal 2004, 403, 410.

1144 Benkard/Jaenstaed, EPÜ, Art. 64, No. 19; also Clark, Vici, Reach-through infringement: what are the limits?, 6 Bio-Science Law Review 2000/2001, 249, 250.

1145 BGH, 11 IIC 236 (1980) – Color Picture Tubes (Farbbildröhre); Benkard/Jaenstaed, EPÜ, Art. 64, No. 24; Benkard/Scharen, Patentgesetz, § 9, No. 53.

1146 Straus, Joseph, Reach-through claims and research tools as recent issues of patent law in: Estudios sobre propiedad industrial e intellectual y derecho de la competencia, Curell Suñol, M./et al. (Eds.): Grupo Español de la AIPPI, Barcelona, 2005, 921, 928.

1147 BGH 8 IIC 147 (1995) – Alkylendiamine I; UK Court of Appeal, 11 IIC 591, 591 (1998) – Pioneer Electronics Capital Inc. v. Warner Music Manufacturing Europe ("Under European law, a product obtained directly by means of a patented process is the product with which the process ends"). A classification of what is considered "directly obtained" is made based on two major approaches, namely the "Chrononological approach" (Chronologischer Ansatz) and the "Theory of Properties" (Eigenschaftstheorie). See Beier, Friedrich-Karl/Ohly, Ansgar, Was heißt "unmittelbares Verfahrenserzeugnis"? - Ein Beitrag zur Auslegung des Art. 64 (2) EPÜ, GRUR Int. 1996, 973. See also Benkard/Scharen, Patentgesetz, § 9, No. 53; Benkard/Jaenstaed, EPÜ, Art. 64, 25.

the direct result of a patented process after having undergone further modifications, provided it retained its identity and did not lose its fundamental characteristics. [1148]

With regard to the subject under consideration, *in-silico* screening processes are directed to the finding of potential binding ligands. Such information is used for drug design. The actual drug, however, is not made out of the *in-silico* screening process. Without being directed to the manufacture of a physical good, *in-silico* screening processes must be considered mere working processes. The screening process does not end with the manufacture of the identified compound, but rather with the acquisition of information about the binding properties of such compound. Identified compounds do not share the identity of the patented screening operation as patented subject matter. In conclusion, patents to *in-silico* screening methods do not provide a patent protection that covers potentially screened compounds.[1149] Thus, uses of identified compounds do not constitute infringement of screening process patents.

2. The Bayer v. Housey Case

U.S. patent law is also familiar with the extension of a process patent to the product which is generated by the process. The Federal Circuit decision *Bayer v. Housey*[1150] raised the question of whether the importing of knowledge that is disclosed with the assistance of a patented process in a foreign country infringes the patented process as such.[1151] The critical law is Section 35 U.S.C. 271 (g) which lays down that "whoever without authority *imports* into the United States … a product, *which is made by a process patented in the United States,* shall be liable as an infringer". [1152] The claim at issue in *Bayer/Housey* reads as follows:

> 1. A method of determining whether a substance is an inhibitor or activator of a protein whose production by a cell evokes a responsive change in a phenotypic characteristic other than the level of said protein in said cell *per se*, which comprises (n steps)
>
> (a) providing a first cell line which produces said protein and exhibits said phenotypic response to the protein;

1148 Bruchhausen, Karl, Sind Endprodukte unmittelbare Verfahrensprodukte eines auf die Herstellung eines Zwischenproduktes gerichtenten Verfahrens?, GRUR 1979, 743, 744.

1149 See Pioneer Electronics Capital Inc. v. Warner Music Manufacturing Europe GmbH [1997] R.P.C. 757; Wolfram, Markus, 'Reach-Through Claims' and 'Reach-Through licensing' - Wie weit kann Patentschutz auf biotechnologische Research Tools reichen?, Mitteilungen der deutschen Patentanwälte 2003, 57-64.

1150 Bayer v. Housey, 340 F.3d 1367-1378 (Fed. Cir. 2003).

1151 Bayer v. Housey, 340 F.3d 1367, 1371.

1152 Bayer v. Housey, 340 F.3d 1367, 1371.

(b) providing a second cell line which produces the protein at a lower level than the first cell line, or does not produces the protein at all, and which exhibits said phenotypic response to the protein to a lesser degree or not at all;

(c) incubating the substance with the first and second cell lines; and

(d) comparing the phenotypic response of the first cell line to the substance with the phenotypic response of the second cell line to the substance.[1153]

Housey alleged that the knowledge *Bayer* obtained from the process of the patent as such is a product. *Bayer* argued that "made" means "manufactured" and that information is not a manufactured creation.[1154] Because of the definition of the term "being made by a process" was ambiguous, the Court interpreted other provisions of the Omnibus Trade and Competitiveness Act of 1988 (which referred to Section 271(g)), finding several indications that the term "made" had to be understood as "manufactured" and applied only to physical goods.[1155] Housey asserted that Congress when said "manufactured" in all cases it was referring to manufacturing. Thus, when saying "made", Congress must have intended something else.[1156] The Federal Circuit was not persuaded, stating that Congress is permitted "to use synonyms in a statue".[1157] The court further stated, "Housey's position suggests an unrealistic level of clarity in congressional word selection"[1158]. Analyzing the legislative history, the court came to the same conclusion that "made" is synonymous to "manufactured". The court further reasoned,

"reading the statue to cover processes other than manufacturing processes could lead to anomalous results. The importation of information … cannot be easily controlled. As Bayer points out, a person possessing the allegedly infringing information could, under Housey's interpretation, possibly infringe by merely entering the country …. Such an illogical result cannot have been intended."[1159]

The court found that if the Congress had intended to give the provision a different meaning, they had to establish appropriate legislation.[1160] The court also considered Housey's assertion that Bayer's drugs were goods made by its proprietary screening methods, holding that the case must be distinguished from *Bio-Technology General Corp. v. Genentech*, where the CAFC had concluded "that a protein made by a host organism expressing an inserted plasmid was a product 'made by' the patented

1153 Bayer v. Housey, 340 F.3d 1367, 1369.
1154 Bayer v. Housey, 340 F.3d 1367, 1371.
1155 See also Liebert, Mary Ann, Information is not physical goods, 22 Biotechnology Law Report 2003, 619-620.
1156 Bayer v. Housey, 340 F.3d 1367, 1373.
1157 Tyler v. Cain, 533 U.S. 656, 664 (2001); Bayer v. Housey, 340 F.3d, 1367, 1373.
1158 Bayer v. Housey, 340 F.3d. 1367, 1373.
1159 Bayer vs. Housey, 340 F.3d., 1367, 1377; see also Paul v. Davis, 424 U.S. 693, 698-99, 96 S.Ct. 1155, 47 L.Ed.2d 405 (1976).
1160 Bayer v. Housey, 340 F.3d 1367, 1376.

process for creating the plasmid itself".[1161] By contrast, the court concluded, the patented process in *Bayer* is not used in the actual design of the drug. As the lower court had noted "processes of identification and generation of data are not steps in the manufacture of a final drug product."[1162] Thus, the Court concluded that the product of *Bayer* does not fall under Section 271(g).[1163] Infringement under Section 271(g), the court explained, is limited to the manufacture of physical goods. It does not extend to knowledge that is generated by a patented process. Therefore, the Court stated that the dismissal of Housey's claims of infringement of patents covering methods of screening compounds that have particular characteristics must be affirmed.[1164] In sum, the reasoning set forth by U.S. courts resembles the situation existing under the EPC and the GPA.[1165] Patents to screening processes do not extend to compounds identified by these screening processes.

VIII. Concluding Remarks

The foregoing shows that patent owners who often find themselves in an interdependent relationship, are able to balance their interests through cross-licensing agreements.[1166] This applies with regard to selection inventions where the broad

1161 Bio-Technology General Corp. v. Genentech, Inc., 80 F.3d 1553, 1561 (Fed. cir. 1996); Bayer v. Housey, 340 F.3d, 1367, 1377-1378.

1162 Bayer AG, 169 F. Supp 2d. at 331; Bayer v. Housey, 340 F.3d 1367.

1163 Liebert, Mary Ann, Information is not physical goods, 22 Biotechnology Law Report 2003, 619-620. The Housey patents were rendered invalid in Housey v. AstraZeneca, 366 F.3d. 1348: Housey sued AstraZeneca alleging infringement of its four patents to screening methods related to protein inhibitors and activators. The district court construed the definition of "inhibitor or activator" to include substances that both directly and indirectly affect a protein of interest. Housey then stipulated that, if this construction were not reversed or modified on appeal, its patents would be invalid and not infringed. The district court came to a final judgment of invalidity and non-infringement. The Federal Circuit held that the claim construction of the district court regarding the "inhibitor or activator of a protein" was properly concluded and thus affirmed the decision. Consequently, the Housey patents were affirmed as invalid and not infringed. One judge (Newman) dissented. Housey, 366 F.3d 1348, 1349.

1164 Bayer v. Housey, 340 F.3d 1367, 1378.

1165 Chapter 4 C VII 1.

1166 Another mechanism by which companies may achieve synergies is the creation of patent pools. This practice allows companies practicing related technologies to assign or license their patents and establish a "clearing house for patent rights", Sung, Lawrence M./Pelto, Don J., The Biotechnology Patent Landscape in the United States as we enter the New Millennium, 1 The Journal of World Intellectual Property 1998, 889-901. In exchange for access to a patent pool, patentees retain their respective patents and license them non-exclusively to others. Licensing is made either directly or through an administrative intermediary created for the purpose. Patent pools are subject to close scrutiny for possible anti-trust violations and therefore must demonstrate that they have strong 'pro-competitive' effects. OECD, Genetic Inventions, Intellectual Property Rights and Licensing Practices, Paris 2002, 66.

claim typically dominates selective improvement.[1167] With regard to identified compounds, patent owners of the screening method can either try to agree on reach-through licensing agreements or – a safer method – determine other means, such as milestone payments.[1168]

A different case arises if the use of 3-D protein structures infringes the patent related to the underlying genetic information. As the above analysis has shown, this occurs provided the protein is obtained recombinantly. As soon as the native protein is used, no dependency is established. This result, having been achieved by an application of traditional legal standards, seems to establish a strong position for the owner of patents related to recombinant technologies. However, the practice of native protein purification recently has undergone tremendous advances.[1169] Hence, novel purification systems that enable the receipt of sufficient protein amounts and quantities might release inventors from the dependency upon earlier issued recombinant protein patents in the near future. Furthermore, protein research that is based on recombinant proteins in many instances will be covered by the research exemption in both the U.S. and Europe.

As for the patents on human gene sequences already issued, it is worth noting that the time factor will provide release of a potential blocking danger. The development of new drugs based on proteomic related knowledge is a time-consuming process. With a patent only providing 20 years of protection (Art. 63(1) EPC), most existing patents will expire before the time drugs based on proteomic research begin to be commercialized on the market. Until then, the research exemption provided under German law[1170] will ensure that researchers adequately proceed with their work.

Advances in the understanding of the complicated patterns of protein folding raises afresh the issue of competitive protein variant use. The awareness that the 3-D structure dedicates the function, rather than the sequence, may mobilize competitors to use sequence-dissimilar proteins bearing same folds, function and effects. To protect inventors from such uses, traditional legal standards developed in the field of protein variants must be modified. Previously, patentees used percent identity approaches with the sequence as reference in order to achieve protection from protein variants. To expand the patent scope to sequence-dissimilar proteins, the sequence reference should be replaced by a reference to the 3-D folding type. In addition, a claim to amino acids may be expanded to sequence-dissimilar proteins conducting the same functions under the doctrine of equivalents. In the U.S., the 'triple-identity-test' is considered an adequate means for the determination of equivalents. This approach requires that persons skilled in the art consider a means equivalent by its 'function', its 'way' and its 'result'. Applied to protein 3-D structures, an equal fold-

1167 Maynard, John T./Peters, Howard M., Understanding chemical patents: a guide for the inventor, Washington, D.C. 1991, 87; assuming that the selective part is the commercially most desirable product.

1168 See Chapter 3 B III 3 c) aa).

1169 Chapman, Tim, Protein purification: Pure but not simple, 434 Nature 2005, 795, 795.

1170 § 11 Nr. 2 GPA.

ing structure satisfies the ‘way-prong’ of the inquiry. A protein bearing a different fold, by contrast, is interpreted to conduct a function differently. In Germany, the country that is used as example for Europe, established principles require the presence of a technical effect identical *and* predictable for a person skilled in the art. The folding type is interpreted as a modified means. A skilled person must rely on all information provided by a patent in a step-by-step fashion and be able to predict which proteins are members of the same structural type. Due to the legal limitations of the doctrine of equivalents and the significant level of complexity required for a determination of equivalents, it is, however, not always predictable as to whether equivalents can be established or not. With this overall uncertainty, inventors might seek broad literal coverage rather than rely upon the doctrine of equivalents.

Chapter 5: Summary and Findings

The aim of this study was to provide a comparative assessment of legal issues at the nexus between intellectual property rights and a central area of modern biotechnology, proteomics. Specifically, the study discusses the patentability of proteomic patent claims, and the scope of protection of biotechnological inventions in the post-genomic, or proteomic, era. The major findings of the analysis can be categorized accordingly, i.e., into findings related to patentability, and into results in the area of the scope of protection. Moreover, the study of proteomics as an issue for intellectual property rights protection yields some more general results. These will conclude this section.

A. Patentability of Proteomic Patent Claims

As to the patentability of proteomic inventions, a first set of results is related to proteins defined by structural properties *per se*. As shown in Chapter 3 B II, both the EPO and the USPTO share similar views regarding proteomic claims directed to the polypeptide as such. Provided that the polypeptide occurs in various folding types, 3-D structures can establish unambiguous parameter constellations despite previous disclosure of the related amino acid. Consequently, novelty can be established according to classical doctrines originating in the field of chemical compounds, such as the principle of unambiguous parameter. In this respect, it is important to note that the legal treatment of chemical patents does specifically refer to 3-D structures. This can be seen in the legal treatment of stereochemistry inventions. Here, novelty can only be established through the description of the specific 3-D *enantiomere*. The sole inclusion of *racemate mixtures* in the patent description does not suffice. Hence, 3-D information or data can serve as important parameter during the typical application process.

In the area of crystalline proteins, it is again a principle from the field of chemistry that helps to distinguish between novel proteomic compounds and the prior art. Novelty is established by the new physical characteristics of protein crystals. In a similar way, claims to selected structural features (such as binding pockets/epitops) achieve novelty according to principles developed for selection inventions. In particular, the selected sub-field must be narrow and sufficiently far removed from the known range illustrated by working examples. Moreover, it must not merely be randomly selected, but should be the result of a more tightly focused selection. Finally, the selected area should not provide a mere embodiment of the prior art description, but, rather, another invention.

A second set of results concerns the area of bioinformatics. In this respect, Chapter 3 B III 1 illustrated the controversial issue of the patentability of so-called *in-silico* screening methods. The European patent system acknowledges patentability and accepts the claim under the requirements for patentable subject matter.[1171] In contrast, the American patent system rejected related claims, finding that merely non-functional, descriptive data was provided, which renders the research results obvious. Surprisingly, the U.S. applies stricter standards for patentability than Europe, even though many critics of intellectual property rights claim that the U.S. system sets looser standards.[1172]

Based on the application of various general principles, the EPO's solution proves to be more coherent. By contrast, the USPTO's findings are subject to criticism, since they do not consider the patent as a whole, but only its computer-related aspects. Such an approach fails to consider the relationship between biological function and the computerized method. The major question is *not* whether a known algorithm is fed with new data, but whether the effect of the *in vivo* biological process that is simulated with this algorithm is non-obvious. [1173] While the EPO's result is consistent with general principles, the reasoning behind it requires some substantial modifications. In particular, the "further technical effect" required by the EPO should not only be derived from software-related aspects, but from the biological function the protein performs *in vivo*.[1174]

In sum, the analysis of bioinformatics claims shows that both offices derive their solutions from the application of principles that were originally used in the area of computer-implemented inventions. However, the nature of proteomic bioinformatics requires a more comprehensive analysis of the invention as such that goes beyond the aspects of computer implementation. Since the protein's functions define the characteristics of the biological binding process, the former must be considered a crucial element of the *in-silico* method. The computer-based visualization of a biological function translates and transfers a biological mechanism into virtual space, where the (*in vivo*) technical effect is reproduced *in silicio*. The patentability requirement of "technical feature" must therefore be derived from the protein's function. Such an approach, in turn, is also consistent with what is interpreted as a further technical effect by the European Board of Appeals.[1175]

A third set of results – demonstrated in Chapter 3 B III 2 - are those involving protein data. Like *in-silico* methods, they are treated under the principles developed for computer-implemented inventions. The application of these rules shows that claims to mere data lack a further technical effect under the European patent system. Similarly, the U.S. patent system considers the claims as abstract ideas, finding that

1171 Chapter 3 B III 1 a) cc) ii.
1172 Chapter 3 B III 1 a) cc) iii.
1173 Chapter 3 B III 1 a) cc) iii.
1174 Chapter 3 B III 1 a) cc) ii.
1175 Chapter 3 B III 1 a) cc) ii.

they establish mere non-functional descriptive material.[1176] Both views consistently apply well-established principles, and should not be disputed on legal grounds. Nevertheless, scientists could argue that the patent offices do not sufficiently take biophysical concepts into account and act in a discriminatory manner. Patent offices allow patents on standard chemical formulae which are, in fact, merely 2-D coordinates of molecules combined together with some standard rules of chemical connectivity. The 3-D coordinates of proteins, by contrast, are not deemed to be patentable, although they too demonstrate standard rules of chemical connectivity between atoms. From a legal perspective, the offices correctly distinguish between computer storable data and the established chemical practice of determining compounds by means of chemical formula. From a scientist's perspective, however, it appears that distinctions are made regarding the patentability of a molecule depending on the dimension in which the coordinates are represented.[1177]

A final group of claims – demonstrated in Chapter 3 B III 3 - deals with the potentially large number of innovations that will be directed to *identified compounds* obtained by *in-silico* screening methods. Patent applicants may seek to cover these compounds by drafting reach-through claims. The claim language is specified in a way that is broad enough to dominate future compound discoveries that can be used for rational drug design. Both offices adopt a similar approach regarding the strategy of reach-through claiming. Claims are treated under strict standards and typically fail due to a lack of enablement. Hence, inventors should handle the method with caution. With strict conditions for both the written description/sufficient disclosure requirement and the enablement factor, it may be advisable to use other approaches such as milestone payments or reach-through licensing methods. [1178]

To meet the patentability requirements of written description/sufficient disclosure and enablement, it is advisable for applicants to disclose theoretical information about the size and shape of binding sites of the computerized method and of corresponding compounds. Claims that define identified compounds by size and shape are not considered as reach-through claims and are generally allowed by patent offices. Inventors, however, must take into account that such claims pose a high risk of being rendered invalid. If only one prior art ligand has the shape and size demonstrated by the claim and therefore would respond to the *in-silico* protein, the claim lacks novelty. With many molecules being reported in prior art, but not defined by size and shape, the concrete risk of annihilation of novelty is difficult to foresee.[1179]

1176 Chapter 3 B III 2 b).
1177 Chapter 3 B III 3 III 2 c).
1178 Chapter 3 B III 3 c) bb).
1179 Chapter 3 B III 3 c) aa), Chapter 3 B IV.

Long before the term proteomics began to dominate biotechnological research, the question of whether the scope of protection of DNA patents would provoke infringements by yet unrealized inventions was discussed extensively. In particular, some observers raised concerns regarding whether the design of new gene-based pharmaceuticals would be hindered by patented gene sequences. When it became clear that the direct applicability of genetic information to medical conditions was indeed somewhat limited, these concerns experienced a revival.[1180] In what form and to what extent do issues of *dependency* between existing patents on gene sequences and other biotechnological inventions arise? What can be said about the likelihood of *infringement* when it comes to gene patents involving the encoded (or recombinantly produced) protein? And how are problems of *competitive use* dealt with? Since proteomics is one of the most important research area in today's biotechnology environment, these questions particularly apply to proteomic inventions. Part C. of Chapter IV. therefore analyzes issues related to patent dependency and infringement - between gene patents and claims related to the 3-D protein structure, and between different protein-related claims.

The results of this analysis can be summarized as follows. First, the *use of naturally purified and naturally obtained crystalline proteins* does not constitute any infringement.[1181] This stands in sharp contrast to *recombinantly produced proteins*, whose 3-D structure inherently falls within the scope of gene patents that declare the encoded protein as its function.[1182] This discrepancy between recombinant production and natural purification/crystallization results from the fact that the patent system rewards the inventors of recombinant technologies for their contributions to the highly efficient production of large quantities of proteins. Naturally occurring proteins are encoded from non-isolated genes and are not related to the patent covering the isolated gene sequence. As long as available purification and separation techniques fail to provide sufficient amounts of high quality proteins, inventors are forced to rely upon recombinant technologies. Therefore, issues of patent dependency cannot be avoided. The temporary limitation of gene patents, however, will pro-

1180 One example is the issue of gene therapy. Gene therapy is a technique for correcting defective genes causing disease development. In most gene therapy treatments, a normal gene is inserted into the genome to replace a disease, causing gene. Despite great promises and high expectations, the approach has yet not proven succesful in clinical trials. In 1999, gene therapy suffered a major setback with the death of 18-year-old Jesse Gelsinger. This patient died shortly after starting the therapy. In 2003, a second child treated in France developed a leukemia-like condition. As a consequence, the FDA placed a temporary halt on all gene therapy trials using retroviral vectors in blood stem cells; see Human Genome Project Information, available at http://www.ornl.gov/sci/techresources/Hu man_Genome/medicine/ genetherapy.shtml; last checked on January 21, 2008. As for the several approaches that may be used for correcting genes, see Straus, Joseph, Patenting Human Genes in Europe - Past Developments and Prospects for the Future, 26 IIC 920 (1995).

1181 Chapter 4 C I; Chapter 4 C III.

1182 Chapter 4 C II.

vide release of a potential blocking danger. Most existing patents to gene sequences will expire before the time drugs based on time-consuming proteomic research begin to be commercialized on the market.

Furthermore, *problems of the competitive use of protein variants – in particular sequence-dissimilar proteins* sharing common folds – have been considered.[1183] The issue is of major importance for several reasons. On a more general level, sequence-dissimilar proteins can be used to exemplify the question of whether patent claims should be interpreted broadly enough to encompass later-arising technologies. More specifically, the awareness that the 3-D structure rather than the sequence is the critical factor in the determination of protein function offers new opportunities to circumvent and devaluate existing patents. In particular, the effects of previously patented drugs can become subject to mimicking.[1184] This is not only a problem from the perspective of current patentees, whose legal rights to protection will be infringed even though they have invested in time- and money-consuming research. It will also hamper future research on specific biotechnological structures. The reason is that findings related to protein effects may become economically useless as soon as they are published. Other firms can cost-effectively (and without running the risk of infringement) replicate functions using a dissimilar sequence. Consequently, incentives to carry out research on protein effects are weakened. The crucial question is thus how patentees can expand their claims to yet unidentified sequence-dissimilar proteins that bear the same functions as the originally patented proteins.

Finally, the issue of sequence-dissimilar proteins can be used to ask whether traditional legal standards developed in the field of protein variants are sufficient to deal with problems of competitive use. In this respect, this study showed that the hitherto applied practices must be modified in order to guarantee an appropriate scope of protection in proteomics. Previously, patentees used a percent identity approach, with the sequence as reference parameter. In order to expand the patent scope to sequence-dissimilar proteins, the reference to sequence should be replaced by a reference to the 3-D folding type. Such a procedure would solve a large number of problems arising from competitive use.[1185]

Another possibility that should be clearly distinguished from this approach is to expand the coverage of a sequence patent by relying on the doctrine of equivalents.[1186] Sequence-dissimilar proteins are then interpreted as later-arising means to achieve the already-described effect of the originally patented protein. For the U.S., the 'triple-identity-test' is considered adequate means for the determination of equivalents. This approach requires that persons skilled in the art consider a means equivalent by its 'function', its 'way' and its 'result'. Applied to protein 3-D struc-

1183 Chapter 4 C IV.

1184 Usually, the problem of patent dependency is not solved through such procedure: the sequence-dissimilar proteins must still be obtained recombinantly in order to achieve large amounts of highly purified substances, so other genetic patents might be infringed.

1185 Chapter 4 C IV 2 c).

1186 Chapter 4 C IV 3 a) dd).

tures, an equal folding structure satisfies the 'way-prong' of the inquiry. A protein bearing a different fold, by contrast, is interpreted as conducting a function in a different 'way'. As a result, equivalents between sequence-dissimilar structures can be established. However, the above-described limitations of the doctrine, such as prosecution history estoppel or the public dedication rule, introduce an element of risk to inventors that rely upon equivalency.

The fact that the doctrine of equivalents is interpreted differently in various countries adds to this uncertainty. In this respect, the dissimilar treatment in Germany and the U.S. is not a major concern. Formally, the U.S. patent law system determines equivalency at the time of infringement, whereas under the German law the time of priority is the decisive factor. However, the German system analyses the person skilled in the art's awareness (of having identified a modified means at the time of priority) to ask whether the identified means were substituted/replaced by the new technology. Thus, both legal systems evaluate the question of equivalents in light of later-arising knowledge. By contrast, the more restrictive approach employed in the U.K. is substantially different. Here, the House of Lords denied equivalency for the new technology of producing proteins by gene activation. If this narrow formulation of equivalents precluding any equivalent protection beyond the "purposive interpretation," is accepted by other European countries, the doctrine of equivalents will be significantly narrowed. In this respect, inventors would be barred from achieving a patent scope corresponding to those granted by U.S. authorities.[1187]

While all these aspects do not imply that sequence-dissimilar proteins are necessarily excluded from equivalent protection, they should increase awareness of the limitations of related strategies used to broaden the patent scope. Due to the previously discussed European developments, the ambiguity that might result from legal limitations in the U.S., and the significant level of complexity required for a determination of equivalency, it is not always predictable whether equivalents can be established or not. With this overall uncertainty, it is suggested that inventors seek broad literal coverage rather than relying upon the doctrine of equivalents. As explained above,[1188] this implies that the alternative - to expand protection by using the 3-D folding type as reference parameter - should be thoroughly considered.

Besides the questions arising in the areas of naturally obtained (crystalline) and sequence-dissimilar proteins chapter IV analyzes *improvement and selection inventions*.[1189] These two arrangements are especially suited for balancing conflicting interests in the post-genomic era. An important characteristic of many proteomic inventions is that they expand and deepen the knowledge of an already patented substance. For example, the folding of a sub-area of a protein is described and analyzed in a more detailed fashion, which ultimately allows for a more target-oriented drug development process. While the previously granted patent may have been too general to imply a specific medical treatment, it continues to represent an important pre-

1187 Chapter 4 C IV 3 c).
1188 Chapter 4 C IV 2 d.
1189 Chapter 4 C VI 1.

condition for further research. Improvement and selection inventions attenuate the resulting tensions between fundamental research and research targeted to specific applications. Combined with an intelligent use of cross-licenses, they represent an important means of balancing inventors' interests. Patent systems in the countries under consideration acknowledge this, and apply generally the same principles, often derived from chemical inventions.

Finally, the scope of protection issues arise in relation to *identified compounds.*[1190] Under both the German and the U.S. patent system, patents for manufacturing processes do not cover compounds obtained through screening. Therefore, the use of screened compounds does not establish infringement of patented screening processes. Under European statutes, a product must be obtained "directly" by means of the patented process to be covered by the patent. A product "directly" obtained from a patented process is the product with which the process ends. With regard to the subject under consideration, the *in-silico* screening operation is the manufacturing process. The question is thus whether identified compounds should be considered the direct result of this operation. The screening process, however, does not end with the identified compound, but with the database search. Thus, the use of identified compounds does not establish any infringement.

In the U.S., the *Bayer v. Housey* case demonstrated that the issue of identified compounds is treated in a similar fashion. The decision dealt with the question of whether the import of therapeutical compounds that were disclosed with the assistance of a patented process in a foreign country infringed the patented process as such under Section 271 (g) U.S.C. The reasoning of the court indicated that the term "made", as stated in the statue, must be understood as synonymous with "manufactured". Further, the patented screening process is not used in the actual design of the drug, because processes of identification and generation of data are not steps in the manufacture of a final drug product. For these reasons, the use of screened and imported compounds does not violate Section 271(g) as long as it is limited to the manufacture of physical goods and does not extend to knowledge that is generated by a patented process.[1191]

C. General Findings

New technologies always raise doubts about whether the patent system is suited for the fostering their advancement without creating excessive inefficiencies. From the preceding analysis, it should be clear that in the case of proteomics, traditional patent categories are often sufficient for coping with the challenges of the new technology. Thus, one of the more general results of this study is that proteomics as a subject matter of patent law should be considered as the continuation of classical protein research, which itself has assumed many legal concepts from the area of

1190 Chapter 4 C VII.
1191 Chapter 4 C VII 2.

chemical patents. These are combined with principles from other biotechnological fields and from the area of computer-implemented inventions to form the new set of principles that govern the IP treatment of the new technology.

The general set of rules and procedures that has developed during recent decades thus seems to be capable of adapting to the changing set of linguistic constructs that characterize modern scientific and economic processes. In fact, one of the most important yardsticks for a modern patent system seems to be whether it is flexible enough to deal with the very dynamic development of new research areas (in this study, genomics, post-genomics, proteomics, bioinformatics), each characterized by its own "language" of scientific communication. As shown in chapters III and IV, the application of existing principles does yield sensible solutions for dealing with issues of patentability and scope of protection in the area of proteomics.

Adequate principles, however, are only part of a successful application to a new technology. The study at hand also shows that the institutional framework of the patent system can and does react in a surprisingly flexible fashion to new types of inventions, and changes the way a scientific field is perceived. In the five years since the completion of the human genome project, the idea that one gene encodes one protein has been replaced by a dynamic view of cell physiology and biochemistry. Shortly thereafter, the focus of the resulting new field of proteomics itself changed markedly. It became clear that the 3-D structure of proteins is one of the major determinants of a protein's function, and perhaps the single most important one. Thus, within a very short period of time, the state of the art itself has experienced several structural breaks. As shown in chapter III, patent offices have quickly adapted to every new development, even in an anticipatory manner. Aided by the general principles that were laid down by legislative bodies and courts, they have succeeded in changing the focus whenever the biotechnological complex changed. It is worth noting that this flexibility was not hampered, but rather facilitated, by the existence of traditional patent categories.

With regard to proteomics, however, the patent system faces more serious and fundamental challenges than mere adoption to new linguistic constructs and to new research fields. Just as any invention that is likely to have spillover effects in terms of further innovation, the patentability of biotechnological compounds forces the patent system to strike a reasonable balance between open access and exclusivity. The tension between these two principles surfaces at various stages of this inquiry, a core topic of which is the multiple dimensions that determine the breadth and scope of a patent claim. Broad patents that cover a wide range of known and unknown protein characteristics and functions lead to *strong ex ante* incentives to invest in research and development. By contrast, narrow patents that preserve the incentives to explore spillovers and new aspects of a known compound are desirable *ex post*, as the economic benefits of newly discovered structural properties accrue to downstream inventors.[1192]

1192 The economic problems that arise due to conflicts between ex ante and ex post efficiency in the area of cumulative inventions (i.e., inventions that build upon each other) is extensively

This tension between *ex ante* and *ex post* optima dominates many debates in the area of IP protection in general, and biotechnological patents in particular.[1193] Did (broad) gene patents hinder further research? How did the patent system react when it became clear that knowledge about a protein's structure may prove to be much more important to the development of medical treatments than knowledge about the encoding gene, at least in the foreseeable future? How does it deal with the fact that scientific developments often lead to a change in perceptions as to what should be patented, and how broad the scope of a patent should be? Since it represents one of the major technologies in the post-genomic era, proteomics is a very good test case to answer these questions. Its study may deliver important insights into the mechanisms which the patent system provides and its flexibility in dealing with novel issues.

When dealing with issues of *ex post* and *ex ante* optimality, it should not be underestimated that governments faced with such fundamental trade-offs are in danger of suffering from problems of dynamic inconsistency.[1194] It would be socially optimal to credibly promise a strong and broad protection of IP rights (to encourage R&D investment, for example, to facilitate the identification of the genome) and to break this promise as soon as research has delivered the result (to facilitate and boost research on new technologies having more direct applications or a higher short-run success probability, like proteomics). The resulting credibility problem can only be solved by establishing a reputation for strong IP protection. At the same time, however, this emphasis on *ex ante* optimality has to be balanced with institutional mechanisms that provide enough flexibility to react to new technological developments and challenges.[1195]

From the analysis above, it seems that the patent system has developed intelligent solutions combining a broad scope of protection with flexible means of reducing the

disucssed in Scotchmer, Suzanne, Standing on the Shoulder of Giants: Cumulative Research and the Patent Law, Journal of Economic Perspective 1991, 29, and Scotchmer, Suzanne, Incentives to Innovate, In: The New Palgrave Dictionary of Economics and the Law; Newman, Peter, ed., McMillan: London, 1998; 273. See also Menell, Peter S., Intellectual Property: General Theories, In: Encyclopedia of Law and Economics, Volume II: Civil Law and Economics; Bouckaert, Boudewijn/De Geest, Gerrit Ed. Edward Elgar: Cheltenham, 1999; 129, who surveys the economic literature on patent law.

1193 Putnam, Jonathan D., The Price we Pay for Drug Research, Innovative Magazine 2004, 26, exemplifies this tension from a legal perspective, using the area of drug development and the trade-off between innovation and competition policy as examples.

1194 The fact that patent law is an area where the danger for dynamic inconsistency and "broken political promises" is especially large was already emphasized in the seminal contribution by Kydland, Finn E./Prescott, Edward C., Rules Rather than Discretion: The Inconsitency of Optimal Plans, 85 Jounal of Political Economy 1977, 473, for which the authors received the Memorial Nobel Prize in Economic Sciences in 2004.

1195 See also Putnam, Jonathan D., The Price we Pay for Drug Research, Innovative Magazine 2004, 26, for an applied treatment. A more formal economic reasoning with close relations to the subject of this thesis can be found in Craven, B. M./Fiala, C./Shiers, A./Steward, G. T., Time Consistency and the Development of Vaccines to treat HIV/Aids in Africa, 8 Economic Issues 2003, 15.

ex post cost of such solutions. For example, those observers who feared that gene patents may create monopoly positions, punishing the downstream inventors of the post-genomic era (i.e. , those who invent on the basis and around genetic information to deliver medical applications), should recognize that the existing institutional framework offers a number of mechanisms that attenuate such problems. Besides the use of cross-licensing, the practice of granting research exemptions, though still hotly debated in the U.S., offers a relatively new but effective means for guaranteeing the free flow of scientific information and the advancement of fundamental research. Moreover, the concept of "non-obviousness", "inventive step" or "Erfindungshöhe" impedes excessively aggressive patenting strategies by limiting patentability to research efforts that provide a significant benefit to society. In the genomic era, this was exemplified when the widespread patenting of ESTs was prevented. In the proteomic era, a number of bioinformatics inventions are already under close scrutiny as to whether they are obvious.

Recapitulating, those who criticize intellectual-property-right protection from an economic perspective, argue that "it has become increasingly clear that excessively strong or poorly formulated intellectual property rights may actually impede innovation". In particular, they claim that "sorting out the relative contribution [of different ideas] to the outcome … can be nearly impossible".[1196] However, these critics should recognize that the patent system has developed a number of principles that are capable of balancing the interest of multiple parties without having to define the exact contribution of single participants in the scientific process. Since its establishment, the patent system's primary occupation has been to deal with innovations. It is therefore not surprising that the legal principles that have developed over a long period of time are an adequate means for protecting current innovators without hampering innovators in fields that have yet to be defined and explored. In this respect, the field of proteomics, though still in its early stages, is an inspiring example.

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