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.