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.