

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 Patents*, 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/pgc.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 Prioritätszeitpunkt noch unbekannten Ersatzmitteln, GRUR 2001, 905.

926 Chapter 2 B III.

927 Masuoka, Kunihiisa, 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 Betaseron⁹³⁴, 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 Infergen⁹³⁵ (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 similarity⁹³⁸, 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 (Insulin lispro Injection) Prescribing information (May 1, 2000), available at <http://pi.lilly.com/human-prescribing.pdf>; TNKase (Tenecteplase) 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" analogs⁹⁴¹ 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 Circuit’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.*, 415 F.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 discussed⁹⁵⁷ 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 F.2d 1164 (Fed. Cir. 1993).

956 *Fiers v. Revel*, 984 F.2d 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 decisive 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-polar⁹⁸² 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 genres 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 Dubaquié, Yves, Fielder, Paul J., Lowman, Henry B., CA 2002.

981 Meyer-Dulheuer, K.-H., Der Schutzbereich von auf Nucleotid- oder Aminosäuresequenzen 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.

lar⁹⁸³ and neutral (Glycine, Asparagine, Glutamine, Cysteine, Serine, Threonine and Tyrosine), (3) acidic⁹⁸⁴ and polar (Asparagine, Glutamate), and (4) basic⁹⁸⁵ 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 having a 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 achieved⁹⁹⁰ 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 & Assoc.*, 904 F.2d 677, 684 (Fed. Cir. 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 artisan 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.

Commentators¹⁰¹⁵ 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-mentioned¹⁰¹⁹ 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* decision¹⁰³² 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 developed 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 rationale 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 at 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 rationale 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 (Kunststoffrohrteil).

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 ischaemic¹⁰⁶⁵ 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/l magnesium chloride.¹⁰⁶⁶ The court ruled that the amount of 4 mmol/l 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* case¹⁰⁶⁸. The decision handed 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) - Custodioli II.

1067 BGH, 34 IIC 197, 202-203 (2003) – Custodioli 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 Aminosäuresequenzen 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 a host cell, whereas *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 Prioritätszeitpunkt noch unbekannten Ersatzmitteln*, GRUR 2001, 905, 907; according to Tilmann, Winfried/Dagg, Nicola, *EU-Patentrechtsharmonisierung I: Schutzzumfang*, 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 genres 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 than 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 genres 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 genres 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.