VI. Use of selective 3-D protein structure parts (Selection inventions)

1. Relationship to patents covering the entire protein

With regard to a selection invention, it is primarily the dependency on the patent that covers the entire protein that has to be considered. Hence, the patent to the genetic sequence is only involved if the entire protein is part of a patented recombinant process. A potential claim to a selective part of a protein has already been analyzed in the case study above,[1105] but shall be introduced again, reading as follows:

> An isolated and purified polypeptide consisting of a portion of protein P starting at one of amino acids 214 to 218 and ending at one of amino acids 394 to 401 of protein P as set forth in SEQ ID NO: 1.[1106]

As introduced above, "selection inventions" claim a narrow range within a broad scope disclosed by the prior art. [1107]Besides determining the "obviousness" of a claim to a selective field of a broader invention, the question of patent dependency is a decisive element of selection inventions. For classification of the problem, the same principles are applied as those used for the treatment of "improvement inventions". Developments of improved versions of drugs are not necessarily directed to a selective part of the earlier invention, but can also cover additional aspects or the broadening of the earlier version. Generally the term "improvement" is used as an "umbrella term" and also includes the cases in which one "invents around" an existing invention, e.g. attempts to advance the existing technique by using different compounds or facilities without touching the scope of the existing patent.[1108] With the high standard of the "obviousness" factor developed in the field of "selection inventions", the inventive step requirement, however, always includes an improvement over the earlier invention, and the prior art, respectively. Thus, even though not all improvements of a drug produce selectivity, each selective invention can be considered as improvement. The same protein can be used in an improved manner due to the disclosure made with regard to the binding pockets. Generally, patent law does not vest in the original patent holder any right to improvements or derivative inventions and new patents can be granted for the selective part if all other requirements are met. In most cases, the selective patent is "blocked" by the original patent holder, meaning that the selection invention cannot be used without a license from the original patent holder whose technology has been incorporated into the improved

1105 Chapter 3 B II 2 a).

1106 European Patent Office, Japan Patent Office, United States Patent and Trademark Office, Trilateral Project WM4, Comparative Studies in New Technologies (Biotechnology, Business Methods, etc.), Report on Comparative Study on Protein 3-Dimensional (3-D) Structure Related Claims, Vienna 2002, 9.

1107 Chapter 3 B II 2 d).

1108 Dow, Kenneth J./Quigley, Traci Dreher, Improvements for handling improvement clauses in IP licenses: an analytical framework, 20 Santa Clara Computer & High Tech. L.J. 2004, 577, 580-581.

entity.[1109] Likewise, the original patent holder is blocked from using the selection invention. Hence, at least one of the patent owners needs a license from the other in order to use the invention. With the threat of mutual patent blocking, it might be advisable for both patent holders to determine the details of patent use by negotiated agreement.[1110]

As for a selection invention, concerns and objectives of both the owner of the broader, and the owner of the narrow, patent are relatively clear. Typically, the patentee of a selection invention involving a protein domain is interested in producing the protein in a recombinant fashion. Even though his invention may have been developed without the use of a recombinant process, e.g., by determining the binding pockets through protein crystallization or *in silico* screening methods, in most cases a large amount of highly purified proteins is required in order to exercise his invention. Thus, he needs to license the use of a recombinant process. If the owner of the recombinant process is interested in using the improvements of the selective parts, cross licensing can be considered. The particular negotiation and defining of improvement clauses is generally a difficult task.[1111] In the case of a selection invention, however, it is still relatively easy. As the improvement must consist of the properties of a selective part of the earlier invention, the improvement clause has to cover all cases in which the use of the improved product was based on selective properties or the earlier patented product.

In the cases in which the improvement is not related to any selective part, but instead to aspects such as other compounds used or protein analogs or variants being developed, licensing clauses might create considerable difficulties. The concerns and objectives of both parties may be quite divergent. For example, a licensor who developed a specific product or process and plans to continue the advancement of this technology may not wish his improvement to automatically be subsumed within his original agreement with the licensee. On the other hand, the licensee might be concerned about the restrictions that are conveyed by the improvement clause, such as typically used obligations, regarding the further exploitation of the improvements. The definition of the term "improvements" is thus an essential element and existing case law still leaves many questions unanswered. In *Deering Milliken*, the court held that a clear definition of what is considered as an improvement requires "clear, deliberate, and appropriate language".[1112]

1109 Dow, Kenneth J./Quigley, Traci Dreher, Improvements for handling improvement clauses in IP licenses: an analytical framework, 20 Santa Clara Computer & High Tech. L.J. 2004, 577, 581.

1110 Dow, Kenneth J./Quigley, Traci Dreher, Improvements for handling improvement clauses in IP licenses: an analytical framework, 20 Santa Clara Computer & High Tech. L.J. 2004, 577, 581.

1111 Brunsvold Brian G./O'Reilley, Dennis P., Drafting Patent License Agreements, 5th ed. Washington D.C. 2004, 99.

1112 Deering-Milliken Research Corp. v. Leesona Corp., 201 F. Supp. 776 (E.D.N.Y. 1962), aff'd 315 F.2d 475 (2d Cir. 1963).

2. The Amgen case

The importance of improvement clauses and their interpretation is illustrated by the Amgen case.[1113] Amgen, a newly founded biotechnology firm, owned two promising drugs, Epogen and Neupogen. Faced with financial problems, the firm did not have sufficient funding to develop the two pharmaceuticals. Due to this pressure, Amgen created the following deal with Ortho Pharmaceuticals. In exchange for a much needed credit of $ 10 million dollars, Amgen conveyed Ortho exclusive worldwide rights to sell ''Epo'' while retaining its own rights to sell ''Epo'' for the kidney dialysis market in the U.S. The deal proved to be a lifesaver for Amgen, but also made the company lose more than two-thirds of the market for its Epogen drug.[1114] A couple of years later, Amgen developed a new-improved version of "Epo", a hyperglycosylated analog of ''Epo'' known as NESP. Amgen alleged the drug to have the advantage of a three-fold longer half-life than the original ''Epo'', resulting in less frequent dosing.[1115] In order to gain access to the lucrative worldwide non-dialysis market that was estimated to amount to at least 1.35 billion in 1998, Amgen argued that NESP was not covered by the 1985 license agreement with Ortho. Ortho countered that NESP was an improvement covered by the agreement to which it had exclusive rights outside the dialysis market. The arbitration panel, which took over the case, finally decided that Amgen had exclusive rights to NESP and that the new analog could not be considered as an improvement covered by the elaborated license. The ruling not only resulted in giving Amgen access to the lucrative market for ''Epo'', but also raised Amgen's shareholder value more than 23%.[1116] The case helped Amgen to develop into one of the world's largest biotechnology firms.[1117]

3. Applicable law

With regard to selection inventions, little difference exists between the U.S. and Europe. As for the European system, the principles applying to a selection invention have already been described above.[1118] Novelty presupposes that the selected subfield is narrow, that it contains sufficient distance to the known range illustrated by

1113 A detailed description of the case can be found in Fürst, Ingeborg, Amgen's NESP victory cuts out Johnson & Johnson, 17 Nature Biotechnology 1999, 124, 124; see also Straus, Joseph, Genpatente: rechtliche, ethische, wissenschafts- und entwicklungspolitische Fragen, Basel, Frankfurt/Main 1997, 50.

1114 Dow, Kenneth J. /Quigley, Traci Dreher, Improvements for handling improvement clauses in IP licenses: an analytical framework, 20 Santa Clara Computer & High Tech. L.J. 2004, 577, 578.

1115 Dow, Kenneth J. /Quigley, Traci Dreher, Improvements for handling improvement clauses in IP licenses: an analytical framework, 20 Santa Clara Computer & High Tech. L.J. 2004, 577, 578.

1116 Fürst, Ingeborg, Amgen's NESP victory cuts out Johnson & Johnson, 17 Nature Biotechnology 1999, 124, 124.

1117 See Amgens' home page available at http://www.amgen.com/, last checked on January 21, 2008.

1118 Chapter 3 B II 2 d).

working examples, that it is not randomly selected, but is the result of a more tightly-focused selection and that it provides not only an embodiment of the prior art description, but also a further invention.[1119] Nonobviousness/inventive step require an outstanding effect, property, or use when compared with compounds in the known generic invention.[1120] Under both systems, European and the U.S., a patent involving a selection invention always depends on earlier issued patents covering the entire subject. Consequently, the use of a patent to a selective protein part automatically infringes the patent directed to the entire protein.[1121]

With regard to general improvement patents, the crucial question is whether the skilled person was able to predict the improved technology. This is questionable, if the considerations leading the skilled person are based on inventive activity.[1122] One receives a patent based on inventive activity, provided that all further patentability requirements are fulfilled. The scope of protection of earlier issued patents might then equivalently expand to the new technology and create dependency. In this event, the later-issued patent will depend on the earlier issued patent. The two German Federal Supreme Court's decisions *Fixing Device II*[1123] and *Segmentation Device for Trees*[1124] have provided rulings on the subject. The first impression is that both rulings appear contradictory. In *Fixing Device II*, the court stated that:

> [t]he scope of protection of a patent can also include such embodiments that make *use of the protected teaching* while also implementing *an inventive further realization;* it is then a dependent invention.[1125]

Headnote No.1 of the decision *Segmentation Device for Trees* by contrast determines that:

> "The extent of protection of a patent according to Sec. 14 of the Patent Act 1981 is in any event no greater than the extent of protection of a patent according to the previously applicable law. It does not comprise *equivalent derivations based on an inventive step.*"[1126]

Hence, any inventive *further realization* that uses the technical teaching of the patented invention results in an infringing act, but an *equivalent derivation based on an inventive step* does not. Accordingly, it is of the essence as to whether the contested embodiment uses and further develops the patented invention or whether it is

1119 Blumer, Fritz, Formulierung und Änderung der Patentansprüche im europäischen Patentrecht, München 1998, 345.
1120 Blumer, Fritz, Formulierung und Änderung der Patentansprüche im europäischen Patentrecht, München 1998, 358.
1121 Meyers, T. C./Turano, T. A./Greenhalgh, D. A./Waller, P. R., Patent protection for protein structures and databases, 7 Suppl Nature Structural Biology 2000, 950, 951. The previously issued patent to the entire molecule may thus also be referred to as the dominant patent.
1122 Kraßer, Rudolf, Äquivalenz und Abhängigkeit im Patentrecht, Tübingen 1998, 516, 527.
1123 BGH, 23 IIC 111(1992) - Fixing Device II (Befestigungsvorrichtung II).
1124 BGH, 26 IIC 261 (1995) - Segmentation Device for Trees (Zerlegevorrichtung für Baumstämme).
1125 BGH, 23 IIC 111 (1992) - Fixing Device II (Befestigungsvorrichtung II).
1126 BGH, 26 IIC 261, 261 (1995) - Segmentation Device for Trees (Zerlegevorrichtung für Baumstämme).

inventively derived. The invention involved in *Fixing Device II*, by contrast, only involved a further development, since the general concept of the invention was used only in a slightly different way.[1127] In contrast, *Segmentation Device for Trees* dealt with the question of equivalent derivation based on an inventive step.[1128] The court emphasized the importance of the principle of legal certainty which *de facto* results in a limitation of the scope of protection. Further developments that have been made on grounds of inventive activity of third parties should not be interpreted as having been encompassed by the original claim language. The patent owner does not profit from the work done by others. [1129] In this respect, the court referred to principles established by the German Federal Supreme Court, namely, that no motivation exists for society to grant protection to an inventor if he has not provided any specific and clearly determined mental activity.[1130] Hence, neither the German Patent Act nor constitutional principles can justify an extension of the scope of protection to an equivalent derivate based on an inventive step that goes further than the patented invention.

None of these decisions, however, specified how the inventive activity should precisely be determined. This missing explanation caused wide-ranging discussions in the literature. General interpretations concluded that it is not contradictory to assume the contested embodiment to be inventive and equivalent at the same time. With the patenting of the contested embodiment and the infringement of the patent not ruling each other out, the mere fact that a patent has been granted for the contested embodiment does not by itself disprove equivalents.[1131]

The decision *Snow Removal Blade*[1132]*,* which dealt with the different embodiments of a snow-crawler bar, brought more clarity to this question. Here, the court distinguished between two different kinds of properties an invention may contain: substituted properties and properties that improve an earlier invention through the addition of further elements. In the event that the substituted property exclusively establishes inventiveness, equivalents must be denied, since a person skilled in the art would not have been able to predict the equal effectiveness.[1133] This rule does not apply in the event that an invention is improved though the addition of further elements/characteristics. In such a case, the principles developed in *Fixing Device II*

1127 BGH 23 IIC 111(1992) - Fixing Device II (Befestigungsvorrichtung II).
1128 BGH, 26 IIC 261, 266 (1995) - Segmentation Device for Trees (Zerlegevorrichtung für Baumstämme).
1129 BGH, 26 IIC 261, 266 (1995) - Segmentation Device for Trees (Zerlegevorrichtung für Baumstämme).
1130 BGH, 26 IIC 261, 267 (1995) - Zerlegevorrichtung für Baumstämme (Segementation Device For Trees).
1131 Meier-Beck, Peter, The Latest Issues in German Patent Infringment Proceedings, 32 IIC 505, 516 (2001).
1132 BGH, 33 IIC 525 (2002) – Snow Removal Blade (Räumschild).
1133 BGH, 33 IIC 525, 531 (2002) – Snow Removal Blade (Räumschild).

continue to be applicable, which results in the conclusion that the contested embodiment falls within the equivalent scope of the earlier granted patent.[1134]

The questions of equivalency and improvement exist under U.S. law as well.[1135] In *Varco L. P. v. Pason,*[1136] the question was whether Varco's claim to an automatic drilling system covered the electronic drilling system later developed by Pason.[1137] Varco alleged that "it first developed an automatic drilling system that uses multiple parameters to regulate the release of the drill string", which is why its patent also covered the electronic system operated by Pason.[1138] The Federal Circuit found the interpretation of claims by the district court, which had denied infringement, to be "unduly restrictive."[1139] The court determined that "because this case seems to present an instance of after-arising technology (e.g., improvements on prior innovations), the district court may find it appropriate to consider infringement under the doctrine of equivalents." [1140]

As under German law, a distinction between improvements that add to the initial patent claim elements and those that substitute for those elements must be made.[1141] Only the latter raises the above discussed problem as to whether equivalency can be found if an ordinary person skilled in the art involves inventive activity in his assumptions. The earlier described *Warner-Jenkinson* decision avoids the question by clearly establishing equivalency as of the date of infringement.[1142] If equivalency is determined at the time of infringement, the inquiry is made in light of later (post-

1134 BGH, 33 IIC 525, 532 (2002) – Snow Removal Blade (Räumschild); Allekotte, Bernd, Räumschild - Neuschnee in der Diskussion über Patentverletzung und efinderische Tätigkeit, GRUR 2002, 472, 475.

1135 Varco L. P. v. Pason, 436 F.3d 1368 (Fed. Cir. 2006), citing the following additional cases: Am. Hosp. Supply Corp. v. Travenol Labs., Inc., 745 F.2d 1, 9 (Fed. Cir. 1984) ("An appropriate range of equivalents may extend to post-invention advances in the art in an appropriate case."); Hughes Aircraft Co. v. United States, 86 F.3d 1566, 1584 (Fed. Cir. 1996), remanded, 520 U.S. 1183, 117 S.Ct. 1466, 137 L.Ed.2d 680 (1997), aff'd, 140 F.3d 1470, reh'g denied, 148 F.3d 1384 (Fed. Cir. 1998), cert. denied, 525 U.S. 1177, 119 S.Ct. 1112, 143 L.Ed.2d 108 (1999) (stating that an inventor is not required to predict all future developments that enable the practice of his invention); SuperGuide Corp. v. DirecTV Enter., Inc., 358 F.3d 870, 880 (Fed.Cir.2004) (quoting SRI Int'l v. Matsushita Elec. Corp. of Am., 775 F.2d 1107, 1121 (Fed. Cir. 1985) (en banc)) ("The law 'does not require that an applicant describe in his specification every conceivable and possible future embodiment of his invention.' "); Smithkline Beecham Corp. v. Excel Pharm., Inc., 356 F.3d 1357, 1364 (Fed. Cir. 2004) (stating that the "quintessential example of an enforceable equivalent" is "after-arising" technology); Glaxo Wellcome, Inc. v. Impax Lab. Inc., 356 F.3d 1348, 1354 (Fed. Cir. 2004) (also concluding that the "quintessential example of an enforceable equivalent" is after-arising technology).

1136 Varco L. P. v. Pason, 436 F.3d 1368 (Fed. Cir. 2006).

1137 Varco L. P. v. Pason, 436 F.3d 1368, 1372.

1138 Varco L. P. v. Pason, 436 F.3d 1368, 1370.

1139 Varco L. P. v. Pason, 436 F.3d 1368, 1376.

1140 Varco L. P. v. Pason, 436 F.3d 1368, 1376.

1141 Sarnoff, Joshua, The Doctrine of Equivalents and Claiming the Future after Festo, 14 The Federal Circuit Bar Journal 2004, 403, 410.

1142 Warner-Jenkinson, 520 U.S. 17, 37.

issuance) knowledge.[1143] Thus, the improvement may be a non-obvious improvement at its time of filing, and yet equivalent in light of later arising knowledge. Later arising knowledge might also cause obviousness of the improvement.

VI. Use of compounds identified through 3-D protein structure screening methods

The final question to be analyzed is whether the use of compounds obtained through an *in-silico* screening process infringes the patent that was granted to the screening process itself. As a first step, a recent case related to compounds that have been identified by a patented method and later been imported into the country where the existing patent was originated will be presented. Then, several approaches to the protection of identified compound will be examined.

1. Protection as product of patentable process

Infringement is constituted if identified compounds can be classified as products of a patented process.[1144] Under Art. 64 paragraph 2 EPC and § 9 paragraph 2 No. 3 GPA, a patent to a patented process "shall extend to the product directly obtained by such process." German and other European courts distinguish between patents directed to manufacturing processes or working processes.[1145] Manufacturing processes aim to make a physical product, and the patent to the process extends to such a product. In contrast, a working process does not result in a product, but is typically conducted for the purpose of achieving an abstract result of an action ("abstrakter Handlungserfolg").[1146] A product which is obtained directly from a patented process is the product with which the process ends.[1147] A compound can still be considered

1143 Sarnoff, Joshua, The Doctrine of Equivalents and Claiming the Future after Festo, 14 The Federal Circuit Bar Journal 2004, 403, 410.

1144 Benkard/Jaenstaed, EPÜ, Art. 64, No. 19; also Clark, Vici, Reach-through infringement: what are the limits?, 6 Bio-Science Law Review 2000/2001, 249, 250.

1145 BGH, 11 IIC 236 (1980) – Color Picture Tubes (Farbbildröhre); Benkard/Jaenstaed, EPÜ, Art. 64, No. 24; Benkard/Scharen, Patentgesetz, § 9, No. 53.

1146 Straus, Joseph, Reach-through claims and research tools as recent issues of patent law in: Estudios sobre propiedad industrial e intellectual y derecho de la competencia, Curell Suñol, M./et al. (Eds.): Grupo Español de la AIPPI, Barcelona, 2005, 921, 928.

1147 BGH 8 IIC 147 (1995) – Alkylendiamine I; UK Court of Appeal, 11 IIC 591, 591 (1998) – Pioneer Electronics Capital Inc. v. Warner Music Manufacturing Europe ("Under European law, a product obtained directly by means of a patented process is the product with which the process ends"). A classification of what is considered "directly obtained" is made based on two major approaches, namely the "Chrononological approach" (Chronologischer Ansatz) and the "Theory of Properties" (Eigenschaftstheorie). See Beier, Friedrich-Karl/Ohly, Ansgar, Was heißt "unmittelbares Verfahrenserzeugnis"? - Ein Beitrag zur Auslegung des Art. 64 (2) EPÜ, GRUR Int. 1996, 973. See also Benkard/Scharen, Patentgesetz, § 9, No. 53; Benkard/Jaenstaed, EPÜ, Art. 64, 25.