

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

NOVO NORDISK PHARMACEUTICALS,)
INC., and NOVO NORDISK A/S,)
)
)
Plaintiffs,)
)
v.) Civ. No. 02-332-SLR
)
)
BIO-TECHNOLOGY GENERAL CORP.)
and TEVA PHARMACEUTICALS USA,)
INC.,)
)
Defendants.)

Frederick L. Cottrell, III, Esquire, and Jeffrey L. Moyer, Esquire, of Richards, Layton & Finger, Wilmington, Delaware. Counsel for Plaintiffs. Of Counsel: Albert L. Jacobs, Jr., Esquire, Daniel A. Ladow, Esquire, Eugene C. Rzucidlo, Esquire, and Joseph M. Manak, Esquire, Elizabeth S. Lapadula, Esquire, Beverly Lubit, Esquire, Magnus Essunger, Esquire, Jenifer Shahan, Esquire, Gaston Kroub, Esquire, of Greenberg Traurig, LLP, New York, New York.

Josy W. Ingersoll, Esquire of Young Conaway Stargatt & Taylor, LLP, Wilmington, Delaware. Counsel for Defendants. Of Counsel: Richard L. DeLucia, Esquire, Steven J. Lee, Esquire, Thomas J. Meloro, Esquire, and John W. Bateman, Esquire, of Kenyon & Kenyon, New York, New York.

OPINION

Wilmington, Delaware
Dated: August 3, 2004

ROBINSON, Chief Judge

I. INTRODUCTION

On April 30, 2002, Novo Nordisk Pharmaceuticals, Inc. and Novo Nordisk A/S (collectively "plaintiffs") filed a patent infringement action under 35 U.S.C. § 271 and §§ 281-285 against defendants Bio-Technology General Corp. and Teva Pharmaceuticals USA, Inc. (collectively "defendants"). (D.I. 1) Plaintiffs allege that defendants willfully infringed claim 1 of U.S. Patent No. 5,633,352 (the "'352 patent") by manufacturing and/or selling or offering to sell their biosynthetic human growth hormone ("hGH") product Tev-Tropin™ in the United States. On May 21, 2002, defendants answered the complaint denying the infringement allegations. Defendants contend that they sold hGH as allowed under 35 U.S.C. § 271(e)(1). Defendants likewise claim that the '352 patent is invalid for failure to comply with the patent laws of the United States and unenforceable due to inequitable conduct. (D.I. 50 at ¶¶ 10, 19, 20) Defendants also filed a declaratory judgment counterclaim pursuant to 35 U.S.C. § 1 et seq seeking a declaration that the '352 patent is invalid, not infringed, and unenforceable. (Id. at ¶¶ 22, 30, 31, 32) The court has jurisdiction over this suit pursuant to 28 U.S.C. §§ 1331, 1338(a).

On May 3, 2002, plaintiffs moved for a preliminary injunction and temporary restraining order to enjoin defendants from selling Tev-Tropin™. (D.I. 5) The court granted

plaintiffs' motion on June 7, 2002.¹ (D.I. 45, 46)

On September 20, 2002, plaintiffs moved to bifurcate the issue of liability from the question of damages for both the discovery and trial phases. (D.I. 65) On November 21, 2002, the court granted this motion in part during oral argument; the court stayed the question of damages pending resolution of liability. (D.I. 82)

On December 6, 2002, plaintiffs filed a motion for summary judgment that defendants' invalidity claims are barred by judicial estoppel. (D.I. 86) On January 23, 2003, defendants filed a cross-motion for summary judgment that their invalidity claims are not barred by judicial estoppel. (D.I. 98) On March 3, 2003, defendants also filed a motion for summary judgment that the claims of the '352 patent are not entitled to the filing date of plaintiffs' PCT Application No. DK 83/00118 ("the 1983 PCT application") under the doctrine of judicial estoppel. (D.I. 116) On April 22, 2003, plaintiffs filed a cross-motion for summary judgment that they are not estopped from claiming the benefit of the filing date of the 1983 PCT action. (D.I. 146) The court denied all motions and cross-motions on June 9, 2003. (D.I. 161, 162)

On June 18, 2003, following summary judgment motions,

¹On June 10, 2002, defendants appealed the court's decision to the United States Court of Appeals for the Federal Circuit. (D.I. 48) On November 29, 2002, the Federal Circuit vacated the grant of a preliminary injunction. (D.I. 84)

defendants amended their answer and counterclaim to add additional allegations to support of their invalidity and unenforceability claims. (D.I. 168 at ¶¶ 20, 31) On July 2, 2003, plaintiffs responded, denying the newly-added allegations. (D.I. 170 at ¶10)

Prior to trial, defendants admitted infringement of claim 1 of the '352 patent. (See D.I. 165, ex. 3, 5) From August 4, 2003 to August 8, 2003, the parties tried the issues of (1) claim construction; (2) invalidity based on anticipation grounds; and (3) unenforceability based on inequitable conduct.² The following are the court's findings of fact and conclusions of law pursuant to Fed. R. Civ. P. 52(a).

II. FINDINGS OF FACT

A. The Parties

1. Novo Nordisk Pharmaceuticals, Inc. is a corporation organized under the laws of the State of Delaware with its principal place of business in Princeton, New Jersey. (D.I. 1 at ¶ 2)

2. Novo Nordisk A/S is a corporation organized under the laws of the Kingdom of Denmark with its principal place of business in Bagsvaerd, Denmark. (Id. at ¶ 3)

3. Novo Nordisk Pharmaceuticals, Inc. and Novo

²Plaintiffs admit that damages are not in dispute because defendants have not sold Tev-Tropin™ in the United States. (See D.I. 201 at 1)

Nordisk A/S are research-based pharmaceutical manufacturers.

4. Bio-Technology General Corp. is a corporation organized under the laws of the State of Delaware with its principal place of business in Iselin, New Jersey. (Id. at ¶ 4)

5. Teva Pharmaceuticals USA, Inc. is a corporation organized under the laws of the State of Delaware with its principal place of business in North Wales, Pennsylvania. (D.I. 50 at ¶ 5)

B. The Technology in General

6. Proteins and peptides consist of chains of amino acids. Bio-Technology General Corp. v. Novo Nordisk A/S, Civ. No. 02-235-SLR (hereinafter "Bio-Technology I") (BTX 3 at 4). The amino acids are selected from the group of about twenty naturally occurring cellular amino acids. (Id.) The left-hand end of the amino acid chain is referred to as the N-terminus, and the right-hand end of the chain is referred to as the C-terminus.

7. Genes are comprised of long chains of DNA, which consist of nucleotide triplets. (Id.) These nucleotide triplets are referred to as codons. (Id.) When a particular protein is to be synthesized, messenger RNA ("mRNA") copy the region of the DNA that codes for the protein (i.e., the codons specific to the protein). (Id.) The mRNA are then used by the cell as a pattern to produce the protein. (Id.)

8. A cell seldomly synthesizes a desired protein directly. (Id. at 5) Rather, the first product, commonly

referred to as a "fusion protein," typically consists of the final protein plus a pro-sequence. (Id.) The pro-sequence consists of additional amino acids attached to the N-terminus of the final desired protein. (Id.) To obtain the final desired protein, proteolytic enzymes cleave the peptide bonds between the pro-sequence and the final desired protein. (Id. at 7)

9. Two types of proteolytic enzymes may be employed in protein synthesis: (1) exoproteases; and (2) endoproteases. Exoproteases cleave amino acids from the end of a protein chain at either the N-terminus or the C-terminus. Endoproteases, in contrast, cleave amino acids in the interior of a protein chain.

10. Aminopeptidases are exoproteases and cleave amino acids from the N-terminus of a protein chain. *Aeromonas*, Aminopeptidase I ("AP I"), leucine aminopeptidase ("LAP"), and dipeptidyl aminopeptidase I ("DAP I") are four distinct aminopeptidases.

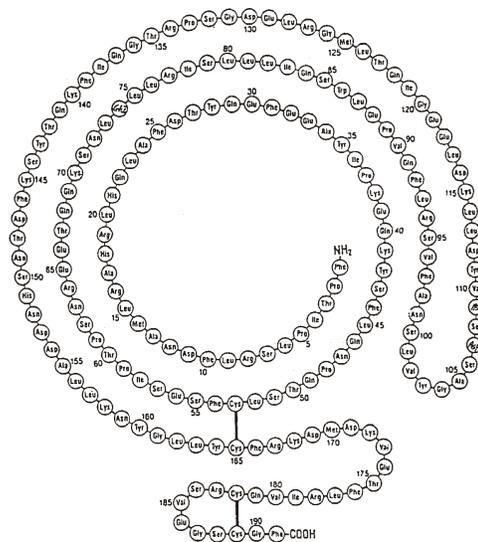
11. LAP has the enzyme classification number E.C. 3.4.11.1. It releases amino acids sequentially one-by-one from the N-terminus of a peptide by hydrolyzing the amide bonds found in the peptide. (Id. at BTX 319) LAP is known to have an optimal pH in the range of 7.5-9.0 and is unstable in the region of 4 to 5. (Id. at BTX 23; BTX 318) If the peptide to be cleaved by LAP contains a proline residue, LAP will not cleave the amino acid that precedes the proline residue because LAP is unable to hydrolyze the bond that exists between the proline

residue and the preceding amino acid. (Id. at DTX 319 at 433)

12. DAP I has the enzyme classification number E.C. 3.4.14.1 and is also referred to as cathepsin C. It releases amino acids sequentially in dipeptidyl units from the N-terminus of a peptide. It is known to have an optimum pH in the range of 4 to 6. (Id. at BTX 23)

C. Human Growth Hormone

13. Human growth hormone ("hGH") is a specific protein consisting of 191 amino acids. It is naturally secreted by the pituitary gland. (Id. at Paper 124 at 2) Proline is the second to last amino acid located at the N-terminus. The amino acid sequence for hGH is shown in the figure below.



14. Human growth hormone is administered to treat conditions such as dwarfism, infertility, wound care, and intoxication. (Id. at BTX 36 at NNG0025821)

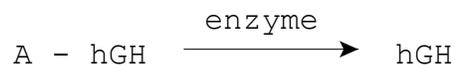
15. Pituitary-derived hGH may contain contaminants

that cause a variety of diseases such as Creutzfeldt-Jakob disease, Gerstmann-Straussler-Scheinker syndrome, and Kuru. ('352 patent, col. 3 at ll. 42-46) The risk of these diseases has lead some countries to ban the use of pituitary-derived hGH. (Biotechnology I at BTX 36 at NNG0025821) For this reason, the need arose to produce hGH synthetically using recombinant DNA technology.

16. There are two basic approaches to make hGH using recombinant DNA technology: (1) an enzymatic cleavage system; and (2) a secretion system.

a. Enzymatic Cleavage System

17. In this approach, the gene for hGH is transferred to a host organism, such as the *E. coli* bacteria. The *E. coli* bacteria are transformed to express the fusion protein consisting of hGH with pro-sequence attached to the N-terminus. ('352 patent, col. 3 at ll. 26-29) The pro-sequence is cleaved from the fusion protein using an exopeptidase to form biosynthetic hGH. The following scheme shows this enzymatic cleavage system:



where A is a pro-sequence. (Bio-Technology I at BTX 23)

18. If LAP is selected as the cleavage enzyme, cleavage terminates at the amino acid preceding proline, as noted above, leaving hGH as the final product. (Id.) The concept of using proline in conjunction with LAP to control the recombinant

DNA synthesis of hGH is referred to as the "Y-pro stop signal strategy."

b. Secretion System

19. In this approach, host organisms such as yeast are transformed so that they express a pre-protein consisting of the desired protein with a leader or signal sequence attached to the N-terminus. The pre-protein is transported through the cell membrane. During transport, an endopeptidase, referred to as a "signal peptidase," clips off the leader sequence. The desired protein then is secreted outside the cell.

20. Human growth hormone is expressed in the human pituitary gland as a pre-protein having a 26-amino acid leader sequence. The pre-hGH is transported through the cell membrane where the 26-amino acid leader sequence is clipped off. The desired 191-amino acid hGH then is secreted outside the human pituitary gland.

D. Novo's '352 Patent

21. The '352 patent, entitled "Biosynthetic Human Growth Hormone," was filed on March 10, 1995.

22. The '352 patent was granted on May 27, 1997.

23. The named inventors include Henrik Dalboge, John Pedersen, Thorkild Christensen, Jorli W. Ringsted, and Torben E. Jessen.

24. The '352 patent traces priority to a series of applications, including: (1) U.S. Application No. 372,692 filed

on January 13, 1995; (2) U.S. Application No. 959,856 filed on November 12, 1992 (the "'856 application"), (3) U.S. Application No. 759,106 filed on September 6, 1991; (4) U.S. Application No. 215,602 filed on July 1, 1988; (5) U.S. Application No. 910,230 filed on February 6, 1986; (4) U.S. Patent Application No. 640,081 filed on August 8, 1984 ("the 1984 U.S. application"); (5) PCT Application PCT/DK83/00118 filed on December 9, 1983 ("the 1983 PCT application"). ('352 patent, col. 1 at ll. 4-16)

25. The '352 patent generally discloses a process to prepare a desired protein. (See '352 patent, col. 1 at ll. 17-19)

26. In particular, the '352 patent describes using an aminopeptidase, preferably DAP I, to cleave a pro-sequence containing an even number of amino acids thereby forming a desired protein. ('352 patent, col. 1 at ll. 56-60)

27. The '352 patent discloses nine examples. Examples 2-4 indicate that DAP I from Boehringer Mannheim was used to cleave the pro-sequence from the desired protein. None of the examples mention using DAP I from Sigma. ('352 patent, col. 4 at ll. 50-col. 5 at ll. 5)

28. The '352 patent includes two independent claims directed to biosynthetic ripe hGH.

29. Claim 1 recites:

Biosynthetic ripe human growth hormone free of contaminants from pituitary derived human growth hormone.

('352 patent, col. 10 at ll. 7-9)

30. Claim 2 recites:

Biosynthetic ripe human growth hormone produced by expressing an amino terminal extended human growth hormone fusion protein in a microorganism capable of such expression, enzymatically cleaving the amino terminal extension and recovering the biosynthetically produced ripe human growth hormone.

('352 patent, col. 10 at 10-15)

31. In May 1997, plaintiffs filed a request for reexamination of the '352 patent based upon a substantial new question of patentability posed by various prior art references including U.S. Patent No. 4,755,465 (the "Gray '465 patent"), U.S. Patent No. 4,775,622 (the "Hitzeman '622 patent"), and U.S. Patent No. 4,745,069 (the "Mayne '069 patent"). (NNX 792 at NNG 0023024; NNG 0023047) Plaintiffs also sought to amend claims 1 and 2 and add new claim 3 as follows:

Claim 1. (Amended) Biosynthetic ripe human growth hormone of **at least 99% purity, which is** free of contaminants from pituitary derived human growth hormone.

Claim 2. (Amended) Biosynthetic ripe human growth hormone produced by expressing an amino terminal extended human growth hormone fusion protein, **wherein the amino terminal extension is negatively charged,** in a microorganism capable of such expression, enzymatically cleaving the amino terminal extension and recovering the biosynthetically produced ripe human growth hormone.

Claim 3. Biosynthetic ripe human growth hormone free of contaminants from pituitary derived human growth hormone, said human growth hormone being of sufficient purity to be administrable to humans.

(Id. at NNG 0023051) (bolded text shows proposed amendment to

claims 1 and 2)

32. In August 1997, the examiner denied the request for reexamination, concluding that the cited prior art did not raise any substantial new questions of patentability. The examiner stated:

The [c]laims of the Dalboge et al. patent, for which reexamination is requested, are directed to ripe human growth hormone (hGH) that is free of pituitary contaminants. The patent defines ripe hGH as having 191 amino acids. . . . Gray et al. do not claim ripe hGH and no interference of claimed subject matter is apparent. . . . [B]ecause Mayne et al. do not cleave the N-terminally extended [growth hormone] with enterokinase and because such cleavage would be expected to remove the N-terminal extension and truncate hGH at amino acid position 172, Mayne et al. do not teach ripe [growth hormone] . . . Hitzeman et al. did not sequence the entire hGH that was secreted from yeast but sequenced only the N-terminal of secreted hGH. The immunoassay used to detect the secreted hGH would not be expected to differentiate between hGH truncated at the C-terminal by yeast proteases and ripe hGH . . . and therefore this argument is sufficient to void Hitzeman et al. as raising a substantial new question of patentability.

(Id. at NNG 0023105)

33. In 2000, plaintiffs engaged in an interference³ with defendants to determine priority of invention for the subject matter of the single interference count⁴ corresponding to

³An interference is an *inter partes* proceeding conducted by the Board of Patent Appeals and Interferences of the United States Patent and Trademark Office ("the Board") to resolve questions of priority of an invention. 35 U.S.C. § 135(a).

⁴"A count defines the interfering subject matter between two or more applications or between one or more applications and one or more patents." 37 C.F.R. § 1.601(f).

claim 1 or claim 2 of the '352 patent.⁵ See Blumberg v. Dalboge, Interference No. 104,422; see also Bio-Technology I; Paper 124. The Board awarded priority of invention to plaintiffs, finding that the 1983 PCT application enabled a species within the scope of the interference count. (Id.) As a result, plaintiffs maintained the '352 patent.

E. The 1982 Danish Application

34. Danish Application No. 5493/82, entitled "A Process For Preparing Ripe Proteins From Fusion Proteins Synthesized in Pro- or Eukaryotic Cells," was filed on December 10, 1982 ("the 1982 Danish application"). (Bio-Technology I; BTX 3)

35. The 1982 Danish application is directed to a process for preparing ripe proteins by, first, expressing in pro- or eukaryotic cells a DNA segment, which codes for the synthesis of a fusion protein and, then, converting the fusion protein produced from the DNA segment to the ripe protein *in vitro*. (Id. at 7-8)

36. The 1982 Danish application generally describes four procedures for preparing desired ripe proteins from fusion

⁵The precise interference count was defined as follows:
A composition of matter according to claims 61, 62, 63,
or 64 of Blumberg (09/023,248)
or
A composition of matter according to claims 1 or 2 of
Dalboge (5,633,352)
(Bio-Technology I; Paper 1)

proteins. (See id. at 8-10) To this end, the 1982 Danish application does not recite any information concerning the reaction conditions, such as pH, time, temperature, or enzyme-to-substrate ratio, to be used for the enzymatic cleavage reactions. The 1982 Danish application merely states: "This cleavage reaction is to be optimized with respect to time and enzyme concentration as, in the case of prolonged incubation, aminopeptidase I can also hydrolyze amino acids of the desired product." (Id. at 9)

37. Similarly, the 1982 Danish application does not specify the identity, length, or sequence of the amino acid pro-sequence. The only guidance provided is that when formyl methionine or methionine is not part of the pro-sequence, the C-terminal amino acid, which is directly bonded to the N-terminal amino acid of the desired protein, must be proline, unless the desired protein itself contains proline as the N-terminal or next-to-the-outermost N-terminal amino acid. (Id. at 10) Besides this information, the 1982 Danish application discloses only that "X is an arbitrary amino acid" when the pro-sequence is X-proline and that "the DNA sequence corresponding to this pro-sequence may be selected from among the large number of naturally occurring sequences or may be synthesized *in vitro* when the structure at the nucleotide and amino acid level is known." (Id. at 8, 9)

38. Lastly, the 1982 Danish application states

"proteases . . . and in particular aminopeptidases" are used to cleave pro-sequences in fusion proteins. (Id. at 8) The 1982 Danish application identifies AP I and LAP as suitable aminopeptidases, but does not disclose a particular supplier of LAP. (Id. at 9, 10)

39. The 1982 Danish application does not contain any examples or experimental data. (Id.)

40. The 1982 Danish application contains eight claims directed to processes for preparing ripe proteins. (Id. at 11-13)

41. Claim 1 recites a process to prepare ripe proteins using recombinant DNA technology. (Id. at 11) Claim 1 does not disclose a particular enzyme to cleave the pro-sequence, but states that the enzyme "stops the cleavage of the amino acids of the pro-sequence one step before proline." (Id.)

42. Claim 7 is dependant upon claim 1 and specifies LAP as the cleavage enzyme. (Id. at 12)

43. Claim 8 is dependent upon claims 1-7 and discloses a process to prepare hGH wherein the pro-sequence is specifically phenyl alanine proline. (Id. at 13)

F. The 1983 PCT Application

44. The 1983 PCT application, entitled "A Process for Preparing Ripe Proteins from Fusion Proteins, Synthesized in Pro- or Eukaryotic Cells," was filed on December 9, 1983 and claims priority to the 1982 Danish application. (Biotechnology I; BTX

11)

45. The named inventors include Thorkild Christensen, Per Balschmidt, Hans Henrik Dahl, and Kim Hejnaes. (Id.)

46. The 1983 PCT application mirrors the 1982 Danish application, except that the 1983 PCT application includes additional disclosure about the amino acid sequence of the fusion protein and five examples that were not part of the 1982 Danish application. (Id. at 6-7, 9-14) The 1983 PCT application also prefers LAP as the aminopeptidase; the 1982 Danish application did not make this preference. (Id. at 6)

47. Example 1 relates to the synthesise of hGH and describes the experimental procedures used to make hGH in the past tense. (Id. at 9) First, Example 1 discloses that the fusion protein having methionine (Met), leucine (Leu), alanine (Ala), valine (Val), and serine (Ser) ("MLAVS") as the pro-sequence was expressed and evaluated to be greater than 98% pure. (Id.) Second, Example 1 indicates that disulfide bridges in the purified fusion protein were reduced and that the resulting disulfide bonds were broken via S-carbamidomethylation as described in a literature reference. Third, Example 1 states that the purified, reduced, and S-carbamidomethylated fusion protein was treated with LAP as described by D.H. Sprekman and A. Light in the presence of urea and aprotinin. (Id. at 11) Example 1 does not identify a supplier of LAP. Finally, Example 1 discloses that reaction mixture was fractionated by ion

exchange chromatography and that the isolated hGH was determined to be 98% pure. (Id.)

48. Dr. Henrik Dalboge wrote the first part of Example 1 (i.e., expression of hGH with the MLAVS pro-sequence), and Mr. Thorkild Christensen wrote the second part of Example 1 detailing the cleavage and purification steps. (See Bio-Technology I; D.I. 64 at 745-46) Mr. Christensen admitted at trial that Dr. Dalboge used past tense to describe the expression step because he actually performed this experimentation. Mr. Christensen also admitted that he had not performed the cleavage and purification steps at the time the 1983 PCT application was filed. (See id. at 747)

49. Example 2 relates to the synthesis of human proinsulin in yeast wherein the pro-sequence was, in order, methionine, leucine, valine, alanine, glycine, and proline. (BTX 11 at 12) Example 2 discloses that LAP was used to cleave the pro-sequence from human proinsulin. (Id.) Example 2, like Example 1, does not identify a supplier of LAP. Example 2 indicates that isolated human proinsulin was "better than 90% pure." (Id. at 12-13)

50. Examples 3-5 relate to the enzymatic cleavage of small peptides with LAP. (Id. at 13-14) Example 3 discloses that the reaction was conducted at a pH of 8.5 and that LAP from Sigma was utilized to cleave the pro-sequence from the small peptide. (Id. at 13) Examples 4-5 do not provide a supplier of

LAP or discuss a specific pH for the cleavage reaction. (Id. at 14)

51. The 1983 PCT application contains four claims. (Id. at 15-16)

52. Claim 1 is directed to a process for preparing ripe proteins by enzymatic cleavage of a fusion protein with an aminopeptidase. (Id. at 15)

53. Claim 2 is dependent upon claim 1 and discloses that LAP is the aminopeptidase. (Id.)

54. Claim 3 is dependent on claims 1 or 2 and specifies that hGH is the desired protein. (Id. at 16)

G. The 1984 U.S. Patent Application

55. The 1984 U.S. application, entitled "Process for Preparing Ripe Proteins from Fusion Proteins, Synthesized in Pro- or Eukaryotic Cells," was filed on August 8, 1984 and claims priority to the 1983 PCT application and the 1982 Danish application. (Bio-Technology I; NNX 322 at 1)

56. The 1984 U.S. application is identical to the 1983 PCT application; it contains the same disclosure and same five examples.⁶ (Id. at 16-33)

⁶At filing, Novo attempted to add a sixth example to the 1983 PCT application describing the production of hGH by cleaving the pro-sequence methionine, phenylalanine, glutamic acid, and glutamic acid ("MFEE") from the fusion protein MFEE-hGH using LAP. (Bio-Technology I; Paper 124 at 9) The cleavage reaction was performed at a pH of 5.0, and acetamide was added to the reaction mixture. (Bio-Technology I; NNX 332 at 39-40) The PTO refused this addition.

57. During the *ex parte* prosecution, Novo abandoned the 1984 U.S. application by failing to respond to the Examiner's letter dated July 8, 1987. (NNX at 81)

H. Defendants' Infringing Product Tev-Tropin™

58. Tev-Tropin™ is "a polypeptide of recombinant DNA origin of 191 amino acid residues It is produced in, and recovered from *E. coli* and has a naturally derived DNA sequence." (NNX 258 at BTG-DEL 58140) Tev-Tropin is "complete[ly] equivalent with the authentic pituitary-derived hormone with respect to the total amino acid sequence." (*Id.* at BTG-DEL 58141)

59. Tev-Tropin is also referred to as Somatropin and BioTropin in the United States. (*Id.* at BTG-DEL 58140)

I. Claim Construction

60. The court construed claim 1 in deciding whether to grant plaintiffs' motion for a preliminary injunction. (*See* D.I. 45) The court concluded that the term "biosynthetic" means that the hGH must be made by recombinant DNA techniques. (*Id.* at 4) The court also concluded that the term "ripe" is used to indicate that the product of the '352 patent has the 191 amino acid sequence identical to that of human growth hormone produced by the human pituitary gland as well as the full biological activity of the human pituitary gland. (*Id.*)

61. Neither party challenged the court's construction of claim 1 during the appeal of the preliminary injunction to the

Federal Circuit. See Novo Nordisk A/S v. Bio-Technology General Corp., 52 Fed. Appx. 142, 144 (Fed. Cir. 2002).

62. The Federal Circuit stated that it understood the court's construction "to mean that the 191 amino acid product exhibits the full biological activity of the growth hormone produced by the human pituitary gland." Id.

63. The specification of the '352 patent discusses "ripe hGH" on four occasions. First, the specification describes a process for preparing hGH disclosed in U.S. Patent No. 4,342,832. "However, this known process results in hGH whose N terminus has attached to it the amino acid methionine which is not present in ripe hGH." (352 patent, col. 1 at ll. 23-25) The specification then discloses an alternate way to produce hGH:

The expression of pre-hGH followed by proteolytic cleavage to obtain ripe hGH in *E. coli* (which is not pathogenic) is indicated in DK Patent Application 2046/84, but it is not documented in that specification that the proteolytic cleavage unambiguously leads to formation of ripe hGH, i.e. with a correct amino acid sequence.

('352 patent, col. 1 at ll. 42-47) Third, the specification describes the benefits of using the Y-Pro stop signal strategy to produce hGH. "The biosynthetic ripe hGH produced is free of all non-hGH pituitary related contaminants including those which cause Creutzfeldt-Jakob disease, and may cause Gerstmann-Staussler-Scheinker Syndrome and Kuru, by virtue of its biosynthetic production." ('352 patent, col. 3 at ll. 42-46) Lastly, the specification further describes the specifics of

using the Y-Pro stop signal strategy: "By selecting an amino extension which contains at least one amino acid with a charged side chain, such as a carboxyl group, it is possible to perform the separation and the purification of amino terminal extended protein from the ripe protein." ('352 patent, col. 3 at ll. 61-65)

64. The abstract of the '352 patent states: "The desired protein is obtained in a pure state. Thus, e.g., hGH without content of Met-hGH may be produced by the process." ('352 patent, abstract)

65. The examples that describe producing hGH using DAP I recite a product of high biological purity. Example 1 states that "[t]he hGH product was shown to be more than 99% pure, evaluated by SDS electrophoresis. . . . The biological activity of the hGH product was determined by a tibia test and was found to be 2.5 IU/mg, which is also the case with authentic hGH." ('352 patent, col. 5 at ll. 31-38) Similarly, Examples 2 and 3 recite that "[t]he hGH product was shown to be more than 99% pure evaluated by IE-HPLC and SDS electrophoresis. . . . The biological activity of the hGH product was determined by a tibia test and was found to be equipotent with pituitary hGH." ('352 patent, col. 5 at ll. 66-67; col. 6 at ll. 5-7, 36-44) Likewise, Example 5 discloses that "[t]he hGH product was shown to be more than 99% pure evaluated by IE-HPLC and SDS electrophoresis." ('352 patent, col. 7 at ll. 6-7)

66. Turning to the prosecution history, plaintiffs discussed "ripe" hGH on multiple occasions. First, in an amendment to the '856 application⁷ filed in 1992 to overcome a rejection under 35 U.S.C. § 103, plaintiffs stated:

Genentech and Eli Lilly have only relatively recently developed a process for producing human growth hormone containing 191 amino acids, i.e., ripe human growth hormone, which does not contain F-Met or Met at the N-terminus. Those companies' processes are not the ones described in [U.S. Patent No. 4,342,832] or in the Goeddel et al. article on which the [e]xaminer relies in this case. As noted above, [a]pplicants were the first to produce ripe human growth hormone.

(BTX 65 at NNG 0023628) Second, in 1994, in an interview agenda associated with the '856 application, plaintiffs identified the distinguishing feature of their invention to be "directed to obtaining ripe human growth hormone, human growth hormone with a correct amino acid sequence." (BTX 65 at NNG 0023535) Third, in an amendment subsequent to the 1994 interview summarizing the topics discussed, plaintiffs argued:

"Ripe" human growth hormone as defined on page 2, line 1 of the specification⁸ is human growth hormone with a correct amino acid sequence. This is synonymous with mature human growth hormone. In contrast to the cited prior art, the ripe hGH made according to the method of the present invention contains a correct N-terminus free of methionine.

(BTX 65 at NNG 0023542-43) Fourth, in a 1995 amendment to U.S.

⁷Recall that the '352 patent is a downstream continuation of the '856 application and claims priority to the filing date of this application.

⁸Page 2, line 1 of the specification of the '856 application corresponds to col. 1, l. 47 of the '352 patent. (See BTX 65 at NNG 0023352; '352 patent, col. 1 at l. 47)

Application No. 372,692,⁹ plaintiffs asserted that “[r]ipe human growth hormone is human growth hormone of 191 amino acids having the identical amino acid sequence to human growth hormone produced from the pituitary gland.” (BTX 65 at NNG 0023673)

67. The PTO likewise commented on the meaning of the term “ripe” in denying plaintiffs’ request for reexamination of the ‘352 patent. The examiner stated that “[t]he patent defines the ripe hGH as having 191 amino acids.” (NNX 792 at NNG0023104)

68. During the interference proceeding, plaintiffs asserted as fact 15 in their preliminary motion 10 that “[t]he ‘352 patent describes “ripe” hGH as having the complete amino acid sequence, i.e., the same amino acid sequence, as pituitary-derived hGH, with full biological activity.” (Bio-Technology I; Paper 36 at 8) Defendants admitted this fact without reservation. (See id.; Paper 61 at 3) Similarly, in its decision, the Board of Patent Appeals and Interferences characterized the technology as follows: “The synthetic hGH claimed by [defendants] and [plaintiffs] is said to have the same biological activity and the same 191 amino acid sequence as hGH secreted by the pituitary gland. . . . Since it is synthetically produced, the claimed hGH is said to be free of pituitary related disease-causing contaminants.” (Bio-Technology I; Paper 124 at 2)

⁹Recall that the ‘352 patent is a direct continuation of U.S. Application No. 372,692 and claims priority to the filing date of this application.

69. On the very same day that plaintiffs filed the application which became the '352 patent (i.e., U.S. Application No. 402,286), plaintiffs submitted a preliminary amendment to add claims with purity limitations. Specifically, plaintiffs added independent claim 4 and dependent claims 5, 6, and 7. These claims recite:

4. Biosynthetic ripe human growth hormone which is free of all pituitary related contaminants.
5. Biosynthetic ripe human growth hormone according to claim 4 in substantially pure form.
6. Biosynthetic ripe human growth hormone according to claim 4 which is at least 90% pure.
7. Biosynthetic ripe human growth hormone according to claim 4 which is substantially pure and which is free of contaminant which cause Jacob-Creutzfeldt disease, Gerstmann-Straussler disease and Kuru disease.

Plaintiffs explained the reason for this amendment as follows:

The instant continuation application is submitted for the purpose of submitting claims to biosynthetically produced ripe human growth hormone in highly pure form. . . . Claim 4 specifies that hGH is free of all pituitary related contaminants. Claim 5 specifies that it is substantially pure. Claim 6 specifies that the purity is at least 90%. Claim 7 specifies that the biosynthetic ripe human growth hormone is substantially pure and is free of contaminants which cause Jacob-Creutzfeldt disease, Gerstmann-Straussler disease and Kuru disease.

(Bio-Technology I; DE 1006 at 047-49) During subsequent prosecution, plaintiffs cancelled claims 4, 5, 6, and 7 and added the two claims which appear as claims 1 and 2 in the '352 patent.

70. In its request for reexamination of the '352 patent, plaintiffs attempted to reinsert the purity

limitations by amendment. Plaintiffs amended claim 1 to include a purity limitation of at least 99%. Plaintiffs also sought to add a new claim 3 to recite a biosynthetic ripe human growth hormone product of sufficient purity to be administrable to humans. (NNX 792 at NNG 0023051) To explain these proposed amendments, plaintiffs asserted:

Claim 1 states that the claimed human growth hormone ("hGH") is at least 99% purity [sic]. Examples 1-4 of the '352 [p]atent state that the hGH was recovered in more than 99% purity. . . . Claim 3 states that the hGH is of sufficient purity to be administrable to humans. The '352 [p]atent makes clear that the human growth hormone produced by the method disclosed is for treatment of humans. Prior to the present invention, it was known to treat children of short stature with pituitary derived human growth hormone.

(Id. at NNG 0023052)

J. Cited References

a. U.S. Patent No. 4,775,622 (the "Hitzeman '622 Patent")

71. The Hitzeman '622 patent, entitled "Expression, Processing and Secretion of Heterologous Protein by Yeast," was filed on November 1, 1982 with Ronald A. Hitzeman and David W. Leung as named inventors. This patent was assigned to Genentech, Inc. and granted on October 4, 1988. (BTX 775) It is a continuation-in-part of U.S. Application No. 355,297 filed on March 8, 1992.

72. The Hitzeman '662 patent discloses the use of recombinant DNA technology to produce a desired protein including hGH. ('662 patent, col. 1 at ll. 11-16; D.I. 184 at 213) In

specific, the Hitzeman '662 patent recites a method for producing hGH in yeast cells using the secretion approach. (Id. at ll. 34-38) Yeast cells in a viable medium are transformed to express hGH with a leader protein attached. (Id.) Upon expression, the pre-protein is transported from the yeast cells. During this transport, the leader sequence is clipped from the pre-protein, allowing the hGH to be secreted into the medium. (Id.)

73. The Hitzeman '622 patent discloses that the hGH produced via the secretion approach in yeast consisted entirely of the 191 amino acid found in pituitary derived hGH, to wit, "all of the medium hGH [i.e., hGH secreted into the medium] is processed faithfully as is done by human cells." ('662 patent, col. 20 at ll. 56-62; D.I. 184 at 216) The Hitzeman '622 patent states: "The product is removed with relative ease from the medium, without need to disruptively disturb the viable yeast cells, and recovered in otherwise native form for use without need to remove unwanted presequence or other artifacts of expression (e.g., the methionine attached to the otherwise first N-terminus amino acid which is an expressional consequence of the AUG translational start signal codon)." ('662 patent, col. 2 at ll. 40-48) Figure 13 likewise shows that the signal peptidase completely cleaved the 26 amino acid leader signal. ('622 patent, fig. 13; col. 4 at ll. 24-25) Additionally, the Hitzeman

'662 patent recites that the Western blotting analysis¹⁰ of the hGH product showed "[a] single band corresponding to mature hGH size." ('622 patent, col. 20 at ll. 54-55) Similarly, the Hitzeman '662 patent explains that Edman degradation analysis¹¹ of the first ten residues of the hGH product following purification by antibody affinity chromatography¹² and high performance liquid chromatography revealed "that nearly 100 percent of the hGH was mature hGH."¹³ ('662 patent, col. 20 at ll. 56-62)

74. The Hitzeman '622 patent discloses that the hGH

¹⁰A Western blot is useful to determine the approximate molecular weight of a protein in a sample that binds to antibodies specific to the protein of interest. To create a Western blot, a sample of proteins is placed on a gel. (D.I. 184 at 292-293) An electrical current is applied. The proteins within the sample separate based upon molecular weight. (Id.) The gel is blotted onto a filter and treated with radiolabeled antibodies specific to the protein of interest. (Id.) The antibodies will bind to any proteins that include the particular amino acid sequence recognized by the antibody. (Id.)

¹¹Edman degradation is a technique used to identify the amino acids within a sequence starting from the N-terminus side of the protein. (Id. at 296-297) Individual amino acids are removed one-by-one through a chemical reaction and analyzed against standards to ascertain their identity. (Id.)

¹²In immunoaffinity chromatography, a mixture of proteins is poured through a column containing antibodies specific to the protein of interest. (D.I. 184 at 294-295) The protein of interest binds to the antibodies. (Id.) The remaining proteins pass freely through the column and are released. (Id.) The column is washed to remove residual impurities. The protein of interest then is eluted and isolated in a single collection. (Id.)

¹³High performance liquid chromatography works on principles similar to immunoaffinity chromatography, except that the proteins are separated based upon affinity for the column matrix instead of affinity for specific antibodies. (Id. at 296)

product, "after purification, is fit for use as intended. For example, human leukocyte interferon product finds use as a human antiviral and/or antitumor agent." ('662 patent, col. 2 at ll. 53-56) The Hitzeman '622 patent does not discuss the use of hGH. The Hitzeman '622 patent also states: "Of enormous advantage is the enablement, by this invention, of obtaining useful, discrete protein product in the cell culture medium, eliminating resort to cell lysis in order to recover product hitherto only accessible from the cell contents, often in a form other than mature." ('662 patent, col. 1 at ll. 32-37)

75. The Hitzeman '662 patent claims a process to produce hGH via yeast expression, processing, and secretion. ('662 patent, col. 22 at ll. 64-65)

b. The 1981 Pavlakis Article

76. In December 1981, George N. Pavlakis published an article, entitled "Expression of two human growth hormone genes in monkey cells infected by simian virus 40 recombinants," in the journal Biochemistry (the "1981 Pavlakis article"). (BTX 1072)

77. The 1981 Pavlakis article describes a method of producing hGH using the secretion approach with monkey kidney cells. In particular, a gene for hGH plus a leader sequence is inserted into monkey kidney cells using the simian virus 40 as a vector. The monkey kidney cells synthesize a protein consisting of hGH with an attached leader sequence. The pre-hGH is transported through the kidney cell membranes. During this

transport, enzymes in the cell membrane clip off the leader sequence, releasing the hGH into the medium surrounding the kidney cells.

78. The 1981 Pavlakis article discloses performing this secretion approach for two different hGH genes, identified as hGH1 and hGH2. (Id. at 7398) The hGH1 gene encodes for the 191 amino acid sequence secreted by the pituitary gland. The hGH2 gene is a variant of the hGH1 gene. It contains fourteen amino acid substitutions. (Id.) This form is thought to be secreted by the human placenta. (D.I. 184 at 338)

79. The 1981 Pavlakis article discusses a variety of tests performed on the two hGH products for characterization purposes. The 1981 Pavlakis article discloses that the structure of the hGH1 and hGH2 products was partially digested by chymotrypsin and separated by gel electrophoresis into bands based upon size. The bands for the synthesized hGH1 and hGH2 products were indistinguishable from the band for pituitary-derived hGH. (Id. at 7400; Fig. 3) The 1981 Pavlakis article also discloses that the hGH1 and hGH2 products were compared against pituitary-derived hGH using isoelectric focusing and nonequilibrium pH gradient electrophoresis gels. (Id. at 7400-7401) The product of the hGH1 gene was indistinguishable from the pituitary-derived hGH whereas the product of the hGH2 gene was distinguishable. (Id.) The 1981 Pavlakis article concludes that "[t]he hGH1 protein, as predicted from the DNA

sequence, appears identical in all respect to the major form of pituitary hGH. In contrast, the hGH2 protein differs from authentic hGH both in its behavior on isoelectric focusing gels and in its low immunoreactivity, yet it binds to hGH receptors quite efficiently." (Id. at 7401)

80. The 1981 Pavalakis article also explains the ability of the hGH1 and hGH2 products to bind to cell surface receptors from the IM-9 cultured human lymphocytes and pregnant rabbit liver membranes. (Id. at 7401; Fig. 5) The hGH1 product was indistinguishable from pituitary derived hGH in both systems. The hGH2 product, in contrast, was 50% as active as the hGH1 product in the lymphocyte assay and 100% as active in the liver membrane assay. (Id.)

c. U.S. Patent No. 4,755,465 (The "Gray '465 Patent")

81. The Gray '465 patent, entitled "Secretion of Correctly Processed Human Growth Hormone in *E. Coli* and *Pseudomonas*," was filed on April 25, 1983 with Gregory L. Gray and Herbert L. Heyneker as named inventors. This patent was assigned to Genentech, Inc. and granted on July 5, 1988. (BTX 753)

82. The Gray '465 patent discloses a method to produce hGH in *E. coli* and *pseudomonas* strains of bacteria by the secretion approach. ('465 patent, col. 1 at ll. 7-12) Specifically, the Gray '465 patent discusses transforming bacteria to express hGH with a leader signal of 26 amino acids

attached to the N-terminus. ('465 patent, col. 3 at ll. 3-18)
The pre-hGH is transported through the bacterial cell membrane into either the periplasm or, alternatively, the cell medium. (Id.) During this transport, the leader signal is clipped off by a signal peptidases enzyme, thereby releasing hGH into the periplasm or medium. (Id.)

83. The Gray '465 patent discloses that "using the process of the invention[,] [hGH] can be obtained free of proteins of human origin, in commercially useful amounts, and without the superfluous methionine in addition to the amino acid sequence of the naturally occurring protein." ('465 patent, col. 3 at ll 14-18)

84. The Gray '465 patent discusses the result of assays performed on the hGH product produced via the secretion approach in the *Pseudomonas aeruginosa* bacteria. The hGH product was analyzed via Western blotting,¹⁴ and the results showed "one major component reactive with anti-hGH which has the same electrophoretic mobility as authentic pituitary hGH." ('465 patent, col. 5 at ll. 33-35) "A minor band of somewhat lesser mobility was also detected and [was] presumably unprocessed pre-hGH." ('465 patent, col. 5 at ll. 35-37)

85. The Gray '465 patent also reports the result of an

¹⁴The '465 patent did not use the specific term "Western blotting" to describe the testing performed on the hGH product. However, Dr. Carol MacLeod, one of defendants' expert witnesses, testified that this was the general technique employed based upon the described procedure. (D.I. 184 at 317-318)

Edman degradation on the hGH product produced via the secretion approach in the *Pseudomonas aeruginosa* bacteria. The 'Gray 465 patent explains that "[t]he major reactive component of the cell extracts was purified to homogeneity by immunoaffinity chromatography and high performance liquid chromatography, and the amino acid sequence of the amino-terminus was determined by the Edman degradation method. . . . It was found to be homogenous and to begin with the sequence Phe-Pro-Thr-Ala in perfect correspondence to the sequence of pituitary hGH." ('465 patent, col. 5 at ll. 38-40; col. 6 at ll. 1-6) The patent, however, contained an error in the sequence identity. The actual identity of the N-terminus of the hGH product analyzed by Edman degradation was Phe-Pro-Thr-Ile, the exact amino acid sequence corresponding to the N-terminus of pituitary derived hGH.¹⁵ (D.I. 184 at 319-320)

86. The Gray '465 patent claims a process to produce hGH via expression, processing, and secretion in a procaryotic cell. ('465 patent, col. 6 at ll. 26-35)

¹⁵Dr. Gregory Gray and others published an article in the Biotechnology journal, entitled "Pseudomonas Aeruginosa Secretes and Correctly Processes Human Growth Hormone," in February 1984 describing the production of hGH in *Pseudomonas aeruginosa* bacteria according to the method set forth in the Gray '465 patent. (BTX 761; D.I. 184 at 323-326) The article disclosed a Western blot showing that the molecular weight of the hGH product approximated the molecular weight of hGH derived from the human pituitary gland. (Id. at 163; Fig. 2) The article also corrected the error in the Edman degradation analysis, stating that the N-terminal sequence was determined to be Phe-Pro-Thr-Ile. (Id. at 163)

d. U.S. Patent No. 4,745,069 (The "Mayne '069 Patent")

87. The Mayne '069 patent, entitled "Cloning Vectors for Expression of Exogenous Protein," was filed on March 6, 1984 with Nancy G. Mayne, J. Paul Burnett, Ramamoorthy Belegaje, and Hansen M. Hsiung as named inventors. It is a continuation-in-part of U.S. Application No. 381,992, filed on May 25, 1982. The March 6, 1984 continuation-in-part added Example 3 and a section entitled "Bioassay" to the disclosure found in the May 25, 1982 parent filing. The Mayne '069 patent was assigned to Eli Lilly and Company and granted on May 17, 1988. (BTX 753)

88. The Mayne '069 patent discloses DNA sequences and recombinant DNA cloning vectors efficient in producing proteins, including mammalian and human hormones, enzymes, and immunogenic proteins. ('069 patent, col. 1 at ll. 10-12; col. 6 at ll. 60-64) The Mayne '069 patent preferences cloning vectors designed for the production of human growth hormone or bovine growth hormone. ('069 patent, col. 6 at ll; col. 7 at ll. 1)

89. In general, the Mayne '069 patent describes: (1) synthesizing a coding sequence recognized by enterokinase;¹⁶ (2) attaching this sequence to the DNA sequence which codes for the desired protein; (3) inserting the resulting recombinant DNA cloning sequence into a bacteria; (4) expressing a fusion protein

¹⁶Enterokinase is a hydrolase enzyme known to cleave a peptide at the carboxyl site of a lysine residue that is preceded by a series of acidic amino acids such as glutamic acid and/or aspartic acid. ('069 patent, col. 6 at ll. 1-14)

for the desired protein in the bacteria; and (5) cleaving the pro-sequence of the fusion protein with enterokinase to produce the desired protein. The Mayne '069 patent states that "[t]he exogeneous protein product is isolated by routine methods from the resulting fermentation broth." ('069 patent, col. 7 at ll. 22-24)

90. Example 1 of the Mayne '069 patent specifically discloses a method to produce hGH with enterokinase as the cleavage enzyme. The Mayne '069 patent recites expressing the fusion protein Met-Phe-Pro-Leu-Asp-Asp-Asp-Lys-hGH in *E. coli*, and purifying and concentrating it using an extraction method and ion exchange chromatography. ('069 patent, col. 14 at ll. 6-17) The Mayne '069 patent then recites treating this concentrated fusion protein with enterokinase to cleave the Met-Phe-Pro-Leu-Asp-Asp-Asp-Lys pro-sequence producing hGH. ('069 patent, col. 14 at ll. 18-27) The Mayne '069 patent explains that samples were removed periodically during the cleavage reaction and examined on an isoelectric focusing gel.¹⁷ ('069 patent, col. 14 at ll. 24-27) The Mayne '069 patent states: "The starting material [i.e., the concentrated fusion protein] has an isoelectric point of 4.3 and can be seen to shift with time to a

¹⁷Isoelectric focusing gel is used to distinguish molecules based upon charge or proteins with different numbers of charged amino acids. (D.I. 184 at 353) Molecules with different charges migrate to different locations on the gel. (Id.)

band having the isoelectric point of [hGH] (4.91)."¹⁸ ('069 patent, col. 14 at ll. 24-27)

91. The Mayne '069 patent discloses that Met-Phe-Pro-Leu-Asp-Asp-Asp-Lys-bovine growth hormone was analyzed for biological activity using the "Tibia Assay." ('069 patent, col. 19 at ll. 26-28) In this experiment, rats were randomized to receive doses of: (1) Met-Phe-Pro-Asp-Asp-Asp-Lys-bovine growth hormone; (2) bovine growth hormone standard obtained from the National Pituitary Agency; or (3) vehicle control. After administering treatment for four days, the rats were sacrificed and their right tibias were removed and measured. Rats who received Met-Phe-Pro-Asp-Asp-Asp-Lys-bovine growth hormone and bovine growth hormone standard showed a similar increase in weight and proximal tibia cartilage width compared with those rats who received control. ('069 patent, col. 20 at ll. 25-31; Table I)

92. The Mayne '069 patent claims a recombinant DNA cloning vector useful for expressing exogenous protein and particularly a cloning vector in which the exogenous protein nucleotide sequence codes for human growth hormone or bovine growth hormone. ('069 patent, col. 20 at ll. 48-68; col. 21 at ll. 1-3)

¹⁸The isoelectric point shifted from a more acidic pH of 4.3 to a less acidic pH of 4.91 presumably as the acidic pro-sequence was cleaved from the fusion protein yielding hGH. (D.I. 184 at 352-254)

e. U.S. Patent No. 5,763,215 (The "Blumberg '215 Patent")

93. The Blumberg '215 patent, entitled "Method of Removing N-Terminal Amino Acid Residues From Eucaryotic Polypeptide Analogs and Polypeptides Produced Thereby," was filed on March 8, 1995 with Shmaryahu Blumberg and Daniela Ben Meir as named inventors. This patent was assigned to Bio-Technology General Corporation and granted on June 9, 1998. (NNX 154) It is a continuation of U.S. Application No. 243,045 filed May 16, 1994, which is a continuation of U.S. Application No. 96,067 filed on July 22, 1993, which is a continuation of U.S. Application No. 873,876 filed on April 22, 1992, which is a continuation of U.S. Application No. 445,911 filed on December 4, 1989, which is a continuation of U.S. Application No. 770,692 filed on August 29, 1985, which is a continuation-in-part of U.S. Application No. 641,488 filed on August 16, 1984. (BTX 249) The Blumberg '215 patent adds Examples VI-XIII to the disclosure found in the August 16, 1984 parent filing (the "Blumberg '488 application"). (See BTX 130; NNX 154)

94. The Blumberg '241 patent and the Blumberg '488 application disclose a method of sequentially removing the N-terminal amino acid residues from an analog of a eucaryotic polypeptide synthesized in a foreign host using an aminopeptidase enzyme. ('241 patent, col. 2 at ll. 42-46; BTX 130 at 0013 at ll. 1-12) As a specific embodiment, the Blumberg '241 patent and

Blumberg '488 application recite removing the N-terminal methionine residue from a human growth hormone analog produced in bacteria with *Aeromonas* aminopeptidase. ('241 patent, col .6 at ll. 1-9; BTX 130 at 0020 at ll. 10-19) As another specific embodiment, the Blumberg '241 patent recites removing the N-terminal methionine residue and its adjacent leucine residue from a human growth hormone analog produced in bacteria with *Aeromonas* aminopeptidase. ('241 patent, col. 6 at ll. 19-29)

95. Example I of the Blumberg '241 patent and the Blumberg '488 application discusses cleavage of the N-terminal methionine residue from Met-hGH by *Aeromonas* aminopeptidase. ('241 patent, col. 8 at ll. 41-68; col. 9 at ll. 1-15; Table I; BTX 130 at 0025) Example 1 states that "[p]olyacrylamide gel electrophoresis of the products reveals no detectable degradation of the hGH." ('241 patent, col. 9 at ll. 8-10; BTX 130 at 0027 at ll. 3-5)

96. Example VI of the '241 patent discusses the cleavage of the N-terminal methionine residue and its adjacent leucine residue by *Aeromonas* aminopeptidase. ('241 patent, col. 14 at ll. 12-43)

97. Example XIII of the '241 patent discusses the biological activity of hGH obtained from Met-hGH following removal of the methionine residue with *Aeromonas* aminopeptidase. The '241 patent states: "The authentic recombinant hGH obtained from Met-hGH by reaction with *Aeromonas* aminopeptidase by

procedures essentially the same as those described in Examples I and V including use of ultrafiltrations to remove free methionine is biologically active and displays high activity. . . . Its immunoreactivity is the same as that of pituitary hormone." ('241 patent, col. 18 at ll. 65-68; col. 19 at ll. 1-6)

98. The Blumberg '241 patent and the Blumberg '488 application explain that "[t]he experiments and results presented . . . clearly demonstrate that *Aeromonas* aminopeptidase rapidly removes the N-terminal methionyl residue from Met-hGH." ('241 patent, col. 19 at ll. 27-29; BTX 130 at 0036 at ll. 1-3)

99. The Blumberg '241 patent and Blumberg '488 application claim a method of removing N-terminal methionyl group from recombinant methionyl human growth hormone produced so as to obtain human growth hormone having the biological activity of naturally-occurring human growth hormone using *Aeromonas* aminopeptidase. ('241 patent, col. 20 at ll. 59-68; BTX 130 at 00420 at ll. 17-24)

f. U.S. Patent No. 4,543,329 (The "Daum '329 Patent")

100. The Daum '329 patent, entitled "Process For the Specific Cleavage of Protein Sequences From Proteins," was filed on July 6, 1982 with Joachim Daum, Gerhard Siewert, Michael Topert, and Hartmut Seliger as named inventors. This patent was assigned to Schering Aktiengesellschaft and granted on September 24, 1985. (BTX 1373) It is a continuation of U.S. Application No. 154,196 filed on May 29, 1980.

101. The Daum '329 patent generally discloses two processes to enzymatically cleave a pro-sequence with the formula (1) Pro-XYZ-Gly-Pro, where Xyz refers to all naturally occurring amino acids contained in the genetic code, or (2) Met-Pro, from a fusion protein using collagenase, aminoacylproline aminopeptidase, proline aminopeptidase, or paraphenylenediamine ("PPDA"). ('329 patent, abstract)

102. The Daum '329 patent mentions using the disclosed processes to produce hGH, but recites that "[a]n apparent limitation of this variation is that when the desired foreign proteins contain at the N-terminal yet another proline as the second amino acid, as is the case for the human growth hormone or for the cattle prolactin, then PDDA would continue digestion to a protein shorter by the proline-containing dipeptide." ('329 patent, col. 3 at ll. 60-65) The Daum '329 patent clarifies, however, that this problem may be averted by first inserting an additional amino acid Zxy into the pro-sequence between the Pro-XYZ-Gly-Pro amino acid chain and the desired protein and performing a three step cleavage reaction with leucine aminopeptidase as the final enzyme. ('329 patent, col. 3 at ll. 66-68; col. 4 at ll. 1-13) The Daum '329 patent also recites that leucine aminopeptidase may be used to cleave the N-terminal methionine residue from proteins containing the sequence Met-Uvw-Pro where Uvw is any amino acid except proline. ('329 patent, col. 4 at ll. 14-17)

103. The Daum '329 patent does not contain any examples or claims specifically directed to the production of hGH.

K. Genentech's Inventive Activity

104. Genentech scientist Dr. Gregory Gray testified that his research group first synthesized hGH using *pseudomonas aeruginosa* pursuant to the secretion approach described in the Gray '465 patent "in the first half of 1982." (D.I. 183 at 163) Dr. Gray also testified that after the Edman degradation results were available verifying the identity of the product as hGH, the scientists celebrated the successful synthesis. (Id.)

105. On June 7, 1982, a Genentech memorandum indicated that hGH was produced both from yeast and from *pseudomonas aeruginosa* bacteria. (BTX 727 at TGG 0011 050199) The memorandum stated that "[s]ecretion from yeast is being given a high priority by molecular biology" and that "experiments should be completed by July 4th." (Id.) The memorandum further indicated that "hGH, which has been secreted from [*p*]seudomonas, will be sequenced the week of the 7th to see if it's free of met." (Id.)

106. On June 4, 1982 and June 9, 1982, Genentech scientist Kathy McKowen ("McKowen") reported in her laboratory notebook that she received two samples of supernatant containing hGH secreted from *pseudomonas aeruginosa*. (BTX 757 at TGG 0001 18185-86) McKowen documented that the two samples, designated "Prep I" and "Prep II," were concentrated and provided to Rod

Keck, another Genentech scientist, for HPLC purification.

107. On June 11, 1982, McKowen documented that after purification by HPLC, specific fractions of Prep II were "given to Henry for sequencing." (BTX 757 at TGG 0001 16188) On that same day, Edman degradation data for the sample, referred to as "Pseudo" hGH, showed that the first seventeen amino acids were identical to the first seventeen amino acids in the sequence for pituitary-derived hGH. (BTX 757 at TGG 0001 16297)

108. On June 11, 1982, Genentech scientist Mike Ross sent a communication indicating that Genentech researchers "expressed pre-hGH in *pseudomonas*" and "processed it to mature hGH" such that "[i]t therefore can have no [methionine]." (BTX 820 at TGG 0011 057249)

109. On June 18, 1982, Dr. Gray prepared a molecular biology update concerning the hGH antibody problem and reported producing three separate yields of hGH using the secretion approach in *pseudomonas*. (BTX 728 at TGG 0011 019664) Dr. Gray stated that the "supernatant hGH appears to be correctly processed and unnicked by cellular proteases." (Id.)

110. On July 1, 1982, Genentech scientist Karen Wion documented in her laboratory notebook that "Greg Gray has been working on expression projects using *pseudomonas aeruginosa*. . . . When human growth hormone was hooked up in this manner, Greg saw secretion of completely processed protein at a fairly high level. We would like to do this for albumin as well." (BTX

III. CONCLUSIONS OF LAW

A. Claim Construction

1. The parties at bar argue that the phrase “ripe human growth hormone” requires a protein having the same amino acid sequence as hGH produced by the pituitary gland. (D.I. 202 at 5) Plaintiffs argue that the phrase also requires that the hGH be biologically active and substantially pure. In response, defendants assert that neither the intrinsic nor extrinsic evidence imposes either of the latter two limitations.

2. Claim construction is question of law. Markman v. Westview Instruments, Inc., 52 F.3d 967, 979 (Fed. Cir. 1995) (*en banc*).

3. In interpreting the claims, a court should begin with the intrinsic evidence of record (i.e., the patent itself, including the claims, the specification, and the prosecution history). Vitronics Corp. v. Conceptronc, Inc., 90 F.3d 1576, 1582 (Fed. Cir. 1996). “Such intrinsic evidence is the most significant source of the legally operative meaning of disputed claim language.” Id.

4. First, a court should look to words of the claims themselves to define the scope of the patented invention. Id. There is a heavy presumption that the claim terms carry their ordinary and customary meanings as would be understood by one of ordinary skill in the art. Markman, 52 F.3d at 986. Put

differently, the court must determine how a person of experience in the field of this invention would, upon reading the patent documents, understand the words used to define the invention. Toro Co. v. White Consol. Indus., Inc., 199 F.3d 1295, 1299 (Fed. Cir. 1999). Dictionaries and scientific treatises may help to supply the pertinent context and usage for claim construction. Tex. Digital Sys., Inc. v. Telegenix, Inc., 308 F.3d 1193, 1201, 1202 (Fed. Cir. 2002).

5. Second, because a patentee may choose to be his own lexicographer and use a term in a manner either more or less expansive than its general usage in the relevant art, the court also should review the specification to determine whether an inventor has used any term in a manner other than its ordinary meaning. Vitronics, 90 F.3d at 1582. The specification may act as a dictionary when it either expressly defines terms used in the claims or when it defines terms by implication. Id.

6. Third, a court may consider the prosecution history of a patent, if in evidence. Id. "The prosecution history limits the interpretation of claim terms so as to exclude any interpretation that was disclaimed during prosecution." Id. (quoting Southwall Tech., Inc. v. Cardinal IG Co., 54 F.3d 1570, 1576 (Fed. Cir. 1995)). That is, a court must look to the prosecution history to determine if the patentee has limited the scope of the claims by disclaiming a particular interpretation during prosecution. Biodex Corp. v. Loredan Biomed, Inc., 946

F.2d 850, 862 (Fed. Cir. 1991).

7. Additionally, if the meaning of a term is not clear from the intrinsic evidence, then a court may consult extrinsic evidence, such as expert testimony, in construing claim terms as they would be understood in the relevant art. Markman, 52 F.3d at 980-81.

8. When construing the claims, courts must take great care to avoid importing unnecessary limitations into the claims from the specification. Amgen Inc. v. Hoechst Marion Roussel, Inc., 314 F.3d 1313, 1325 (Fed. Cir. 2003). "If we once begin to include elements not mentioned in the claim in order to limit such claim . . . we should never know where to stop." Johnson Worldwide Assocs., Inc. v. Zebco Corp., 175 F.3d 985, 990 (Fed. Cir. 1999) (quoting McCarty v. Lehigh Val. R.R., 160 U.S. 110, 116 (1895)). Nevertheless, a court should look to the specification to determine whether it refers to a limitation only as a part of less than all possible embodiments or whether it suggests that the very character of the invention requires the limitation be a part of every embodiment. It is impermissible to read the one and only disclosed embodiment into a claim without other indicia that the patentee so intended to limit the invention. Teleflex, Inc. v. Ficoso N. Am. Corp., 299 F.3d 1313, 1327 (Fed. Cir. 2002). On the other hand, where the specification makes clear at various points that the claimed invention is narrower than the claim language might imply, it is

entirely permissible and proper to limit the claims. SciMed Life Sys., Inc. v. Advanced Cardiovascular Sys., Inc., 242 F.3d 1337, 1345 (Fed. Cir. 2001).

9. After reviewing the language of claim 1 (i.e., biosynthetic ripe human growth hormone free of contaminants from pituitary derived human growth hormone) in accordance with the above principles of claim construction, the court construes this claim to mean a protein produced by recombinant DNA techniques composed of a 191 amino acid sequence identical to that of hGH produced by the human pituitary gland with the full biological activity of hGH produced by the human pituitary gland, and free of the contaminants present in hGH produced by the human pituitary gland.

10. One of skill in the art at the time the '352 patent application was filed would have understood the term "biosynthetic" to mean that the human growth hormone must be made by recombinant DNA techniques, consistent with its ordinary meaning.

11. In contrast, the term "ripe" did not have a widely-understood meaning to those of skill in the art at the time the '352 patent application was filed. The court, consequently, turns to the intrinsic evidence to ascertain the meaning of this term.

12. The specification implies that the term "ripe" refers to hGH with an amino acid sequence identical to that of

hGH produced by the human pituitary gland. The specification states: "However, this known process results in hGH whose N terminus has attached to it the amino acid methionine which is not present in ripe hGH." (352 patent, col. 1 at ll. 23-25) In so contrasting the hGH produced by the "known process" with "ripe hGH," the specification suggests that "ripe hGH" consists only of the 191 amino acid residues present in the hGH produced by the human pituitary gland and does not have any additional amino acid residues (e.g., methionine) attached to its N-terminus. Similarly, the specification also refers to ripe hGH as "ripe hGH, i.e. with a correct amino acid sequence." ('352 patent, col. 1 at ll. 47) This language virtually defines "ripe hGH" to mean hGH having the same amino acid sequence as the hGH produced by the human pituitary gland.

13. The prosecution history of the '352 patent supports this definition for the term "ripe." In four instances, plaintiffs argued that "ripe" hGH was human growth hormone of 191 amino acids having the identical amino acid sequence to human growth hormone produced from the pituitary gland. The PTO examiner also adopted this meaning and referred to it in deciding plaintiffs' request for reexamination of the '352 patent. The Board likewise used this definition in characterizing the technology in dispute during the interference proceeding.

14. Besides imparting a sequence identity limitation, the term "ripe" also relates to the biological activity of the

claimed product. If the claimed hGH has the same amino acid sequence as the hGH produced by the human pituitary gland, the court reasons that it implicitly has the same biological activity as hGH produced by the human pituitary gland.

15. The specification supports this interpretation. In all examples, the tibia test results show that the hGH product is equipotent with the hGH produced by the human pituitary gland.

16. The prosecution history also affirms this construction. During the interference proceeding, plaintiffs claimed as a fact and defendants agreed that the biosynthetically-produced ripe hGH has the full biological activity of pituitary-derived hGH. The Board also described the invention of the '352 patent as having the same biological activity as hGH secreted by the pituitary gland.

17. Contrary to plaintiffs' argument, the term "ripe" does not impart a purity limitation. First, if the term "ripe" meant "substantially pure" as suggested by plaintiffs, there would be no need for the language "free of contaminants from pituitary derived human growth hormone" because, by definition, "ripe hGH" would not be contaminated in any way.

18. Additionally, in submitting dependent claims 5, 6, and 7 via preliminary amendment during the prosecution of the '352 patent, plaintiffs attempted to narrow the scope of claim 4, which is identical in scope to claim 1 of the '352 patent, by way of various purity limitations. The juxtaposition of independent

claim 4 without any reference to a purity with dependent claims 5, 6, and 7 that add a purity limitation suggests that independent claim 4 was not intended to contain a purity limitation. Indeed, the Federal Circuit has stated that the presence of a dependent claim that adds a particular limitation raises a presumption that the limitation in question is not found in the independent claim. See Wenger Mfg., Inc. v. Coating Mach. Sys., Inc., 239 F.3d 1225, 1233 (Fed. Cir. 2001) ("Claim differentiation . . . is clearly applicable when there is a dispute over whether a limitation found in a dependent claim should be read into an independent claim, and that limitation is the only meaningful difference between the two claims."); see also Sunrace Roots Enter. Co. v. SRAM Corp., 336 F.3d 1298, 1302-03 (Fed. Cir. 2003) (the presumption that an independent claim does not have a limitation that is introduced for the first time in a dependent claim "is especially strong when the limitation in dispute is the only meaningful difference between an independent and dependent claim, and one party is urging that the limitation in the dependent claim should be read into the independent claim."). Given this presumption and the absence of evidence to rebut it, claim 1 of the '352 patent cannot be construed as having a purity limitation.

19. Furthermore, in attempting to amend claim 1 of the '352 patent to include a 99% purity limitation and add a new claim 3 to recite a "sufficient purity to be administrable to

humans" limitation during reexamination, plaintiffs established that the term "ripe" does not implicate a purity limitation. If it did, then both the proposed amendment and the new claim would have been unnecessary and redundant.

20. Lastly, the court is not persuaded that construing the term "ripe" as having a purity limitation is required based upon the purity disclosure contained within the examples and the abstract. The court finds that these discussions of purity are directed to the "free from hGH contaminants" limitation already expressly recited in claim 1. Indeed, the abstract nearly mirrors the language of claim 1 stating "hGH without content of Met-hGH may be produced by the process." ('352 patent, abstract) Accordingly, the court concludes that it would be improper to construe the term "ripe" as imparting a purity limitation.

B. Claim Preclusion

21. Before delving into the substance of defendants' invalidity defense premised on anticipation grounds, the court shall consider plaintiffs' argument that defendants are precluded from raising an anticipation defense on the ground that they could have raised it by motion under 37 C.F.R. § 1.633(a) during the interference proceeding.

22. Claim preclusion bars a party from litigating in a subsequent action an issue that was or could have been raised by the party in a finally adjudicated prior action. Allen v. McCurry, 449 U.S. 90, 94 (1990). Claim preclusion attaches when

there has been "(1) a final judgment on the merits in a prior suit involving (2) the same parties or their privies and (3) a subsequent suit based on the same causes of action." Churchill v. Star Enters., 183 F.3d 184, 194 (3d Cir. 1999) (quoting United States v. Athlone Indus., Inc., 746 F.2d 977, 983 (3d Cir. 1984)). Claim preclusion has the "dual purpose of protecting litigants from the burden of relitigating an identical issue with the same party or his privy and of promoting judicial economy by preventing needless litigation." Parklane Hosiery Co., Inc. v. Shore, 439 U.S. 322, 326 (1979).

23. The court is unpersuaded by plaintiffs' argument that defendants could have raised their anticipation defense during the interference proceeding. The purpose of the interference proceeding was to determine priority of invention of the subject matter of the interference count, not to invalidate the '352 patent. For this reason, defendants had no motivation to address or even consider the validity of the '352 patent. The validity of the '352 patent, in fact, did not become an issue until plaintiffs sued defendants for patent infringement, almost two years after the interference proceeding.

24. Additionally, the court finds that the third element requisite to invoking the doctrine of claim preclusion is not satisfied. That is, the cause of action adjudicated in the interference proceeding is not in issue in the instant litigation. In the interference proceeding, the parties

addressed the issue of priority of inventorship of the subject matter of the count pursuant to 35 U.S.C. § 146. In contrast, the parties at bar are litigating the issues of invalidity based on anticipation and unenforceability due to inequitable conduct. Accordingly, the court concludes that the doctrine of claim preclusion does not bar defendants' invalidity defense premised on anticipation grounds.

C. Invalidity

25. Defendants assert that the '352 patent is invalid based upon anticipation under 35 U.S.C. §§ 102(a), (e), and (g). "A patent shall be presumed valid." 35 U.S.C. § 282. To overcome this presumption, the party challenging a patent, as defendants do at bar, must prove facts supporting a determination of invalidity by clear and convincing evidence. Apotex USA, Inc. v. Merck & Co., 254 F.3d 1031, 1036 (Fed. Cir. 2001), cert. denied, 534 U.S. 1172 (2002) (citing Am. Hoist & Derrick Co. v. Sowa & Sons, Inc., 725 F.2d 1350, 1360 (Fed. Cir. 1984)). Based upon this teaching, defendants bear the burden of clearly and convincingly proving anticipation.

a. Enablement With an Eye Toward the Priority Date of Claim 1 of the '352 Patent

26. As a precursor to addressing defendants' anticipation argument, the court first must determine the priority date of claim 1 of the '352 patent. Put differently, the court must determine whether claim 1 of the '352 patent is

entitled to the benefit of the filing date of the 1982 Danish application, the 1983 PCT application, or the 1984 U.S. application in order to ascertain which references cited by defendants qualify as prior art against the '352 patent. This inquiry depends on whether the 1982 Danish application, the 1983 PCT application, or the 1984 U.S. application enables the full scope of claim 1 of the '352 patent. If these references are not enabling, then claim 1 of the '352 patent may trace priority of invention only to March 10, 1995, the filing date of the '352 patent.

27. The statutory basis for the enablement requirement is found in 35 U.S.C. § 112, paragraph 1, which provides in relevant part:

The specification shall contain a written description of the invention and of the manner and process of making and using it, in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same.

28. To satisfy the enablement requirement, a specification must teach those skilled in the art how to make and to use the full scope of the claimed invention without undue experimentation. Genentech, Inc. v. Novo Nordisk A/S, 108 F.3d 1361, 1365 (Fed. Cir. 1997). "While every aspect of a generic claim certainly need not have been carried out by the inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention." Id. at 1366. The specification

need not teach what is well known in the art. Hybritech v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1384 (Fed. Cir. 1986).

29. The Federal Circuit has explained that "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable ... Tossing out the mere germ of an idea does not constitute enabling disclosure." Genentech, 108 F.3d at 1366.

30. Enablement is determined as of the filing date of the patent application. In re Brana, 51 F.3d, 1560, 1567 n. 19 (Fed. Cir. 1995).

31. The use of prophetic examples does not automatically make a patent non-enabling. The burden is on one challenging validity to show by clear and convincing evidence that the prophetic examples together with the other parts of the specification are not enabling. Atlas Powder Co. v. E.I. DuPont de Nemours & Co., 750 F.2d 1569, 1577 (Fed. Cir. 1984).

32. Some experimentation may be necessary in order to practice a claimed invention; the amount of experimentation, however, "must not be unduly extensive." Id. at 1576.

33. As summarized by the Patent and Trademark Office Board of Appeals:

The test for whether undue experimentation would have been required is not merely quantitative, since a considerable amount of experimentation is permissible,

if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the invention claimed.

PPG Indus. Inc. v. Guardian Indus. Corp., 75 F.3d 1558, 1564 (Fed. Cir. 1996) (quoting Ex parte Jackson, 217 U.S.P.Q. 804, 807 (1982)).

34. A court may consider several factors in determining whether undue experimentation is required to practice a claimed invention, including: (1) the quantity of experimentation necessary; (2) the amount of direction or guidance disclosed in the patent; (3) the presence or absence of working examples in the patent; (4) the nature of the invention; (5) the state of the prior art; (6) the relative skill of those in the art; (6) the predictability of the art; and (7) the breadth of the claims. In re Wands, 858 F.2d 731, 737 (Fed. Cir. 1988).

35. The enablement requirement is a question of law based on underlying factual inquiries. Id.

36. Before considering the question of enablement as it bears upon identifying the relevant prior art for anticipation purposes, the court finds it instructive to review the issues raised by the parties in a separate litigation tried before this court. In Bio-Technology I, the parties appealed the decision of the Board in Blumberg v. Dalboge, Interference No. 104,422 pursuant to 35 U.S.C. § 146 (the "146 action"). Specifically,

plaintiff Bio-Technology General Corp. ("BTG") appealed the award of priority of invention for the subject matter of the interference count corresponding to biosynthetic ripe hGH to defendants Novo Nordisk A/S and Novo Nordisk Pharmaceuticals, Inc (collectively "Novo"). BTG argued that the '352 patent was not entitled to the filing date of the 1983 PCT application because the 1983 PCT application failed to enable a species within the scope of the interference count. The court agreed with BTG and concluded that the 1983 PCT application is not enabled because one of ordinary skill in art would not have been able to produce biosynthetic ripe hGH at the time the application was filed using the disclosed information. (See Bio-Technology I, D.I. 100) The court also observed that its holding applied to the 1982 Danish application as well because the 1982 Danish application contains nearly the same disclosure as the 1983 PCT application, minus the additional disclosure about the amino acid sequence of the fusion protein and the five examples. (See id.)

37. In the litigation at bar, the court is asked to decide whether the 1982 Danish application, the 1983 PCT application, or the 1984 U.S. application enable the full scope of claim 1 of the '352 patent. This inquiry is much broader than the one presented in the 146 action, to wit, enablement of a species within the scope of claim 1 versus enablement of the full scope of claim 1. Since the court previously concluded that the 1983 PCT application failed to enable a species within the scope

of claim 1, the 1983 PCT application cannot enable the full scope of claim 1. Therefore, the court concludes that claim 1 is not entitled to the benefit of priority of the filing date of the 1983 PCT application or the filing date of the 1982 Danish application.

b. Identification of the Prior Art

38. Under 35 U.S.C. § 102(a), "a person shall be entitled to a patent unless the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the application for patent."

39. Under 35 U.S.C. 102(e),

a person shall be entitled to a patent unless an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent . . . or a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent.

40. Defendants assert that the Pavlakis 1981 article anticipates the invention described in claim 1 of the '352 patent based upon the second activity enumerated in 102(a) (i.e., that the invention claimed in the '352 patent was described in a printed publication before plaintiffs' date of invention on March 10, 1995).¹⁹ Defendants also assert that the Hitzeman '622

¹⁹Notably, § 102(a) and § 102(e) focus on the patent applicant's date of invention. The parties appear to agree for purposes of this opinion that plaintiffs' date of invention is the earliest effective filing date to which plaintiffs are entitled to the benefit of priority of invention. In light of

patent, the Gray '465 patent, the Mayne '069 patent, the portion of the Blumberg '215 patent disclosed in the Blumberg '488 application, and the Daum '329 patent are § 102(e) prior art as they all were filed in the United States before plaintiffs filed the '352 patent on March 10, 1995. The court agrees with defendants and concludes that all of the references cited by defendants qualify as prior art against the '352 patent under 35 U.S.C. § 102. Thus, the court shall consider the potential anticipatory effect of these references on claim 1 of the '352 patent.

c. Anticipation Under 35 U.S.C. § 102(a) and 35 U.S.C. § 102(e)

41. A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. Verdegaal Bros., Inc. v. Union Oil Co., 814 F.2d 628, 631 (Fed. Cir. 1987).

42. A single prior art reference may expressly anticipate a claim where the reference explicitly discloses each and every claim limitation. However, the prior art need not be ipsissimis verbis (i.e., use identical words as those recited in the claims) to be expressly anticipating. Structural Rubber Prods. Co. v. Park Rubber Co., 749 F.2d 707, 716 (Fed. Cir. 1984).

43. A single prior art reference also may anticipate a

the preceding analysis, the earliest date to which plaintiffs are entitled to priority of invention is March 10, 1995.

claim where one of ordinary skill in the art would have understood each and every claim limitation to have been disclosed inherently in the reference. Continental Can Co. USA Inc. v. Monsanto Co., 948 F.2d 1264, 1268 (Fed. Cir. 1991). The Federal Circuit has explained that an inherent limitation is one that is necessarily present and not one that may be established by probabilities or possibilities. Id. That is, "the mere fact that a certain thing may result from a given set of circumstances is not sufficient." Id. The Federal Circuit also has observed that "inherency operates to anticipate entire inventions as well as single limitations within an invention." Schering Corp. v. Geneva Pharms. Inc., 339 F.3d 1373, 1380 (Fed. Cir. 2003). Moreover, recognition of an inherent limitation by a person of ordinary skill in the art before the critical date is not required to establish inherent anticipation. Id. at 1377.

44. An anticipation inquiry involves two steps. First, the court must construe the claims of the patent in suit as a matter of law. Key Pharms. v. Hercon Lab. Corp., 161 F.3d 709, 714 (Fed. Cir. 1998). Second, the finder of fact must compare the construed claims against the prior art to determine whether the prior art discloses the claimed invention. Id.

45. Even if the prior art discloses each and every limitation of set forth in a claim, such disclosure will not suffice under 25 U.S.C. § 102 if it is not enabling. In re Borst, 345 F.2d 851, 855 (1965). "Long ago our predecessor court

recognized that a non-enabled disclosure cannot be anticipatory (because it is not truly prior art) if that disclosure fails to 'enable one of skill in the art to reduce the disclosed invention to practice.'" Amgen Inc. v. Hoechst Marion Roussel, Inc., 314 F.3d 1313, 1354 (Fed. Cir. 2003) (citations omitted). The patentee bears the burden to show that the prior art reference is not enabled and, therefore, disqualified as relevant prior art for an anticipation inquiry. Id. at 1355.²⁰

46. With this framework in mind, the court turns to consider the anticipatory effect of each of the six aforementioned prior art references on claim 1 of the '352 patent. The court notes at the outset that the Hitzeman '662 patent, the Gray '465 patent, and the Mayne '069 patent were considered by the examiner during the reexamination of the '352 patent and the examiner found that these references did not raise substantial new questions of patentability. The Federal Circuit has observed that

[w]hen no prior art other than that which was considered by the PTO examiner is relied on by the attacker, he has the added burden of overcoming the deference that is due to a qualified government agency presumed to have properly done its job, which includes one or more examiners who are assumed to have some expertise in interpreting the references and to be familiar from their work with the level of skill in the art and whose duty it is to issue only valid patents.

Ultra-Tex Surfaces, Inc. v. Hill Bros. Chem. Co., 204 F.3d 1360,

²⁰The court previously discussed the legal standard for enablement above. (See infra, Section III, C, a)

1367 (Fed. Cir. 2000) (citations omitted). In light of this teaching, the court accords great weight to the examiner's evaluation of the Hitzeman '662 patent, the Gray '465 patent, and the Mayne '069 patent references as they relate to claim 1 of the '352 patent.

47. After independently engaging in a thorough review of each of the cited art references, the court finds that the Hitzeman '662 patent, the Gray '465 patent, the Mayne '069 patent, the portion of the Blumberg '215 patent disclosed in the Blumberg '488 application, and the Daum '329 patent do not anticipate each and every limitation of claim 1 of the '352 patent as construed by the court. In particular, the court finds that these references do not disclose either one or both of the limitations triggered by the term "ripe" in claim 1 (i.e., sequence identity and full biological activity). The court will consider each of these references in turn below.

48. The Hitzeman '622 patent discloses that the hGH product is composed of the same 191 amino acid sequence as pituitary-derived hGH. While the Hitzeman '622 patent does not expressly offer data either fully characterizing the entire sequence of the hGH product or the C-terminus as plaintiffs contend is required to prove anticipation, this reference discloses other experiments which, taken in the aggregate, necessarily lead to the conclusion that the amino acid sequence of the hGH product is identical to that of pituitary-derived hGH.

Edman degradation analysis revealed that the leader protein consisting of twenty-six amino acid residues was completely cleaved from the pre-protein, leaving only the desired hGH protein. Edman degradation also characterized the first ten amino acids of the desired protein, establishing that those residues mirrored the first ten amino acid residues in pituitary-derived hGH. Moreover, Western blotting analysis showed that the hGH product exhibited the same "fingerprint" as pituitary-derived hGH.

49. Despite disclosing the sequence identity limitation of claim 1, the Hitzeman '662 patent does not disclose that the hGH product has the full biological activity of hGH produced by the human pituitary gland. At most, the Hitzeman '662 patent states that the hGH product is fit for its intended use after purification. (See '662 patent, col. 2 at ll. 53-56) The court, however, does not read this statement as inherently disclosing that the hGH product is equipotent with pituitary-derived hGH. This statement merely suggests that the hGH product could be used to treat growth hormone diseases, such as dwarfism, without any reference to the expected therapeutic effectiveness. For this reason, the court concludes that the Hitzeman '662 patent does not render the '352 patent invalid under 35 U.S.C. § 102(e).

50. The Gray '465 patent discloses that the hGH produced via the secretion approach in *Pseudomonas aeruginosa*

bacteria was composed of the 191 amino acid sequence identical to that of hGH produced by the human pituitary gland. Like the Hitzeman '662 patent, the Gray '465 patent does not expressly recite that the hGH product exhibits 100% sequence homology with pituitary-derived hGH. The Gray '465 patent, however, inherently makes this disclosure through the collective experimental data. Edman degradation analysis confirmed the homology of the first four amino acid residues of the N-terminus of the hGH product with the first four amino acid residues of the N-terminus of pituitary-derived hGH. Western blotting analysis likewise showed that the hGH product exhibited the same "fingerprint" as pituitary-derived hGH. Nevertheless, the Gray '465 patent does not contain any disclosure concerning whether the biological activity of the hGH product equals that of hGH produced by the human pituitary gland. In fact, the Gray '465 patent does not contain any biological testing data or other reference to the potency of the hGH product. The court, therefore, concludes that this reference fails to teach each and every limitation of claim 1 and cannot invalidate the '352 patent under 35 U.S.C. § 102(e).

51. The Mayne '069 patent fails to disclose both the sequence identity and the biological activity limitations of claim 1 of the '352 patent. Although the Mayne '069 patent discloses cleaving the fusion protein with enterokinase, it contained no disclosure, other than isoelectric focusing gel analysis, to confirm the identity of the hGH product. The court

finds that this isoelectric focusing gel data, in isolation with other experimental evidence such as Edman degradation or Western blotting analyses, only establishes by probability that the hGH product consists of the same 191 amino acid sequence as pituitary-derived hGH because it only measured a pH shift. Additionally, while the Mayne '069 patent discusses the tibia assay, which plaintiffs advocate to be one of the only ways of positively establishing biological activity, it does so only in association with bovine growth hormone product, not a human growth hormone product. Such testing has no relevancy to the biological activity of hGH. The court, consequently, concludes that the Mayne '069 patent does not anticipate claim 1 of the '352 patent pursuant to 35 U.S.C. § 102(e).

52. The portion of the Blumberg '215 patent disclosed in the Blumberg '488 application does not disclose that the hGH produced by cleavage of methionine from Met-hGH using *Aeromonas* aminopeptidase is composed of a 191 amino acid identical to that of hGH produced by the human pituitary gland, even though it expressly claims that the hGH product has the same biological activity as naturally-occurring hGH. Example 1 of this prior art reference only reveals the desired hGH protein was not degraded during the cleavage reaction removing the N-terminal methionine from Met-hGH. (See '241 patent, col 9 at ll. 8-10; BTX 130 at 0027 at ll. 3-5) Example 1 does not recite any characterization of the hGH product (e.g., Edman degradation or Western blotting

analyses) to confirm the identity of the amino acids in the sequence. The specification also merely states that *Aeromonas* aminopeptidase rapidly removes the N-terminal methionyl residue from Met-hGH without further elaborating on the sequence characterization of the hGH product. Accordingly, the court concludes that the portion of the Blumberg '215 patent disclosed in the Blumberg '488 application is not anticipatory prior art under 35 U.S.C. § 102(e).

53. The Daum '329 patent fails to disclose either the sequence identity or the biological activity limitations of claim 1 of the '352 patent. The Daum '329 patent sets forth the Y-stop proline strategy with LAP as the cleavage enzyme. This reference only mentions using this strategy to produce hGH as one example of its utility. The Daum '329 patent does not specifically discuss the nature of the hGH produced using this strategy. There likewise is no inherent disclosure that leads the court to conclude that the hGH product would be composed of the precise 191 amino acid sequence of pituitary-derived hGH or that the hGH product would have the full biological activity of pituitary-derived hGH. As such, the Daum '329 patent cannot render the '352 patent invalid under 35 U.S.C. § 102(e).

54. In contrast to the other five prior art references, the court finds that the Pavlakis 1981 article recites each and every limitation of claim 1 of the '352 patent. First, the Pavlakis article describes a method to produce hGH in

monkey kidney cells using the secretion approach, to wit, recombinant DNA techniques. Second, the Pavlakis 1981 article specifically discusses experimental tests used to characterize the hGH product. Gel electrophoresis, isoelectric focusing, and nonequilibrium pH gradient electrophoresis analyses all revealed that the hGH product was indistinguishable from pituitary-derived hGH. To this end, the Pavlakis 1981 expressly stated:

Figure 3 shows that both proteins gave rise to identical [3H]leucine-containing chymotryptic peptides and that these comigrated with the peptides obtained from unlabeled pituitary hGH. These data, in conjunction with the fact that the intact proteins comigrate with pituitary hGH on NaDodSO₄ gels, suggest that the amino-terminal signal sequences have been appropriately removed.

(BTX 1072 at 7400) This collective data establishes that the hGH product necessarily must be composed of the same 191 amino acid residues as the pituitary-derived hGH. Third, the Pavlakis 1981 article discloses through receptor binding assay data that the hGH1 product exhibited the same receptor binding affinity as pituitary-derived hGH in both the human lymphocyte line IM-9 and the pregnant rabbit liver membranes. From this, the court concludes that the hGH1 product has the full biological activity of hGH produced by the human pituitary gland. Finally, the aforementioned data inherently establishes that the hGH product is free of contaminants present in hGH produced by the human pituitary gland. Accordingly, the court concludes that the 1981 Pavlakis article clearly and convincingly discloses all of the limitations of claim 1 of the '352 patent.

55. Before reaching the ultimate conclusion of anticipation under 35 U.S.C. § 102(a), however, the court must consider whether the Pavlakis 1981 article enables the subject matter of claim 1. In this regard, the court finds plaintiffs have not met their burden of showing that this prior art reference fails to teach one of ordinary skill in the art how to make biosynthetic ripe hGH free of the contaminants from pituitary derived hGH using recombinant DNA techniques without undue experimentation. Plaintiffs have not proffered any concrete evidence concerning why the methodology disclosed in the 1981 Pavlakis article would not lead to the production of hGH. Instead, plaintiffs center their argument on speculation. That is, plaintiffs contend that if the 1981 Pavlakis article disclosed an enabling method to make 191 amino acid hGH having full biological activity of pituitary-derived hGH, then scientists surely would have taken advantage of this method. Because this did not occur and a patent application corresponding to the 1981 Pavlakis article was abandoned, plaintiffs jump to the conclusion that the 1981 Pavlakis article did not present an enabling disclosure. The enablement requirement, however, is not premised on whether the general scientific community adopts a disclosure. Prior art references are presumed to be enabling. Proctor & Gamble Co. v. Nabisco Brands, Inc., 711 F. Supp. 759, 772 (D. Del. 1989) (citing In Re Sasse, 629 F.2d 675, 681 (C.C.P.A. 1980)). Moreover, the Pavlakis 1981 article offers

particular materials and methodology to produce hGH. The court has no reason to doubt that this information will not lead to the successful production of hGH. Indeed, Dr. Pavlakis actually made the subject matter of claim 1 using the disclosed materials and methodology set forth in the Pavlakis 1981 article. The court, consequently, concludes that the Pavlakis 1981 article adequately enabled the subject matter of claim 1 of the '352 patent as of March 10, 1995, the filing date of the '352 patent. As such, the court concludes that the 1981 Pavlakis article renders the '352 patent invalid under 35 U.S.C. § 102(a).

d. Anticipation Under 35 U.S.C. § 102(g)–Prior Invention

56. Under 35 U.S.C. § 102(g)(2), an applicant is not entitled to a patent if "before the applicant's invention thereof the invention was made in this country by another who had not abandoned, suppressed, or concealed it."

57. The Federal Circuit has explained that "if a patentee's invention has been made by another, prior inventor who has not abandoned, suppressed, or concealed the invention, § 102(g) will invalidate that patent." Apotex USA, Inc. v. Merck & Co., 254 F.3d 1031, 1035 (Fed. Cir. 2001). The Federal Circuit also has observed that § 102(g) "retains the rules governing the determination of priority of invention." Hybritech, Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1376 (Fed. Cir. 1986) (quoting Kimberly-Clark Corp. v. Johnson & Johnson, 745 F.2d

1437, 1444 (Fed. Cir. 1984)). To this end, a party alleging prior invention can establish that he was the first to invent by showing either: (1) he was first to reduce the invention to practice; or (2) he was first to conceive the invention and then exercised reasonable diligence in attempting to reduce the invention to practice from a date just prior to the applicant's conception to the date of his reduction to practice. 35 U.S.C. § 102(g) ("In determining priority of invention . . . there shall be considered not only the respective dates of conception and reduction to practice of the invention, but also the reasonable diligence of one who was the first to conceive and last to reduce to practice, from a time prior to conception by the other.") As recognized by the Federal Circuit,

[a] principal purpose of § 102(g) is to ensure that a patent is awarded to a first inventor. However, it also encourages prompt public disclosure of an invention by penalizing the unexcused delay or failure of a first inventor to share the "benefit of the knowledge of [the] invention" with the public after the invention has been completed.

Checkpoint Sys. v. United States Int'l Trade Comm'n, 54 F.3d 756, 761 (Fed. Cir. 1995) (citing Paulik v. Rizkalla, 760 F.2d 1270, 1280 (Fed. Cir. 1985)).

58. Conception is the "formation in the inventor's mind of a definite and permanent idea of the complete and operative invention, as it is hereafter to be applied in practice." Hybritech, 802 F.2d at 1376 (citations omitted). A conception must encompass all limitations of the claimed

invention, and "is complete only when the idea is so clearly defined in the inventor's mind that only ordinary skill would be necessary to reduce the invention to practice, without extensive research or experimentation." Singh v. Brake, 317 F.3d 1334, 1340 (Fed. Cir. 2002) (citations omitted). Put differently, every limitation must be shown to have been known to the inventor at the time the invention is alleged to have been conceived. Davis v. Reddy, 620 F.2d 885, 889 (C.C.P.A. 1980) (citing Schur v. Muller, 372 F.2d 546, 551 (1967); Anderson v. Anderson, 403 F. Supp. 834, 846 (D. D.C. 1975)). Because conception is a mental act, "it must be proven by evidence showing what the inventor has disclosed to others and what that disclosure means to one of ordinary skill in the art." In re Jolley, 308 F.3d 1317, 1321 (Fed. Cir. 2002) (quoting Spero v. Ringold, 377 F.2d 652, 660 (C.C.P.A. 1967)). The Federal Circuit has opined that a court should apply the "rule of reason" in determining conception. That is, the court should examine, analyze, and evaluate reasonably all pertinent evidence when weighing credibility of an inventor's story. Holmwood v. Sugavanam, 948 F.2d 1236, 1239 (Fed. Cir. 1991). Evidence in the form of documents does not need to be corroborated. Id. Rather, "only the inventor's testimony requires corroboration before it can be considered." Price v. Symsek, 988 F.2d 1187, 1195 (Fed. Cir. 1993).

59. Reduction to practice may either occur actually or constructively. Actual reduction to practice requires a showing

by the inventor that "the invention is suitable for its intended purpose." Mahurkar v. C.R. Bard, Inc., 79 F.3d 1572, 1578 (Fed. Cir. 1996). This may require actual testing for a complicated invention or may require only the complete construction of a prototype for a simple invention with obvious purpose and workability. Id. For a party alleging prior invention to establish that he actually reduced his invention to practice by testimony, he must corroborate his proffered testimony with independent evidence, which is evaluated under a rule of reason considering all the evidence. Loral Fairchild Corp. v. Matsushita Elec. Indus. Corp. Ltd., 266 F.3d 1358, 1363 (Fed. Cir. 2001). Notably, there is no requirement that the "prior invention" be commercialized in order for it to be actually reduced to practice. Steinberg v. Seitz, 517 F.2d 1359, 1363 (C.C.P.A. 1975). The key is whether the invention can be commercialized or has reached the point where "practical men [would] take the risk of commercializing the invention." Goodrich v. Harmsen, 442 F.2d 377, 383 (C.C.P.A. 1971). Constructive reduction to practice, in contrast, occurs when a party alleging prior invention files a patent application on the claimed invention. Hybritech, 802 F.2d at 1376.

60. The party alleging prior invention must be able to show diligence "from a date just prior to the other party's conception to . . . [the date of] reduction to practice [by the party first to conceive]." Monsanto Co. v. Mycogen Plant Sci.,

Inc., 261 F.3d 1356, 1369 (Fed. Cir. 2002); Mahurkar, 79 F.3d at 1577. However, it is not necessary for a party alleging prior invention to drop all other work and concentrate solely on the particular invention involved. Rines v. Morgan 250 F.2d 365, 369 (C.C.P.A. 1957). There also need not be evidence of activity on every single day if a satisfactory explanation is offered.

Monsanto, 261 F.3d at 1369 (citations omitted). Additionally, determining whether the required "reasonable diligence" has been satisfied involves specific inquiry. Id. (citations omitted).

61. In order to avoid a finding that a prior invention was abandoned, suppressed, or concealed, the party alleging prior invention must take affirmative steps to make the invention publicly known. Friction Div. Prods., Inc. v. E.I. DuPont de Nemours & Co., 658 F. Supp. 998, 1013 (D. Del. 1987) (citing Ralston Purina Co. v. Far-Mar-Co, Inc., 586 F. Supp 1176, 1215 (D. Kan. 1984)). The Federal Circuit has explained that,

when determining whether an inventor has abandoned, suppressed, or concealed an invention, a period of delay between completion of the invention and subsequent public disclosure may or may not be of legal consequence. The delay may be inconsequential if, for example, it is reasonable in length or excused by activities of the inventor. Furthermore, there is no particular length of delay that is per se unreasonable. Rather, a determination of abandonment, suppression, or concealment has "consistently been based on equitable principles and public policy as applied to the facts of each case." A court must determine whether, under the facts before it, any delay was reasonable or excused as a matter of law.

Checkpoint, 54 F.3d at 761 (citations omitted).

62. Finally, the party alleging prior invention must

establish prior invention by clear and convincing evidence. Apotex, 254 F.3d at 1037-38. If the party alleging prior invention does so, then the burden of production shifts to the patentee to produce evidence sufficient to create a genuine issue of material fact as to whether the party alleging prior invention abandoned, suppressed, or concealed the invention. Id. If the patentee carries this burden of production, then the party alleging prior invention may rebut the evidence of abandonment, suppression, or concealment with clear and convincing evidence. Id.

63. The court finds that Genentech was neither (1) the first to reduce the invention of claim 1 of the '352 patent to practice nor (2) the first to conceive of the invention of claim 1 of the '352 patent and to exercise reasonable diligence in reducing it to practice. The evidence of record concerning Genentech's inventive activities shows only that Genentech utilized a secretion system in *pseudomonas aeruginosa* bacteria to synthesize some form of hGH in June 1982. While Dr. Gray testified that he produced hGH and defendants offered documentation in the form of internal memoranda and laboratory notebook entries to support his testimony, none of the evidence of record provides confirmation of the entire sequence identity for his hGH product. Edman degradation analysis confirmed only the first seventeen amino acid residues without considering the identity of the remaining 171 amino acid residues. Moreover,

there is absolutely no biological evidence of record to establish that the hGH product possessed the full biological activity of pituitary-derived hGH. The court, consequently, concludes that defendants have not proven by clear and convincing evidence that Dr. Gray invented biosynthetic ripe human growth hormone free of contaminants from pituitary derived human growth hormone as recited in claim 1 of the '352 patent. The court declines to find the '352 patent invalid on prior invention grounds under 35 U.S.C. § 102(g).

D. Obviousness-Type Double Patenting

64. In their post-trial briefing, defendants argue that the '352 patent is invalid under the judicially-created doctrine of obviousness-type double patenting over U.S. Patent No. 5,618,697 (the "'697 patent"), which issued on April 8, 1997 from U.S. Application No. 08/372,692. Notably, the '352 patent claims priority to and is a direct continuation of the '697 patent. Claim 1 of the '697 patent recites a detailed process to produce ripe hGH. The '697 patent issued approximately two months before the '352 patent.

65. Obviousness-type double patenting is "judicially created and prohibits an inventor from obtaining a second patent for claims that are not patentably distinct from the claims of the first patent." In re Lonardo, 119 F.3d 960, 965 (Fed. Cir. 1997).

66. The purpose of obviousness-type double patenting

is to prevent an unjustified extension of the right to exclude others from practicing an invention granted by a patent by allowing a second patent claiming an obvious variant of the same invention to issue to the same owner. In re Berg, 140 F.3d 1428, 1431-32 (Fed. Cir. 1998) (citing In re Goodman, 11 F.3d 1046, 1052 (Fed. Cir. 1993)).

67. Generally, the Federal Circuit has applied a "one-way" test to determine obviousness-type double patenting. Berg, 140 F.3d at 1432. Under this test, the application claims are compared for obviousness against the earlier-issued patent claims. Id. In In re Braat, 937 F.2d 589, 592 (Fed. Cir. 1991), the Federal Circuit announced a "two-way" test because of the unusual facts of the case.²¹ The two-way test essentially applies the one-way test in both directions; i.e., (1) the earlier-issued patent claims are compared for obviousness against the application claims; and (2) the application claims are compared for obviousness against the earlier-issued patent claims. Id. When the two-way test is applied, some claims may be allowed that otherwise would have been rejected under the one-way test. Berg,

²¹The Court of Customs and Patent Appeals, a predecessor court to the Federal Circuit, also applied an analysis similar to that used in Braat at various times to determine obviousness-type double patenting. See In re Borah, 354 F.2d 1009 (C.C.P.A. 1966); In re Calvert, 97 F.2d 638 (C.C.P.A. 1938). These cases dealt with the particular situation where the patent applicant filed for a basic invention first and then later filed for an improvement. Through no fault of the applicants, the PTO decided the applications in reverse order of filing, rejecting the first application although it would have been allowed if the applications had been decided in the order of their filing.

140 F.3d at 1432. Notably, the primary basis for the Braat decision - different inventive entities - was removed by the Patent Law Amendments Act of 1984. Id. This test, nonetheless, continues to survive and litigants often dispute which of the two tests to apply.²² Id.

68. In Studiengesellschaft Kohle mbH v. N. Petrochemical Co., 784 F.2d 351, 355 (Fed. Cir. 1986), the Federal Circuit refused to consider the issue of obviousness-type double patenting where the patent challenger "offered no evidence of the scope and content of the prior art, other than [the earlier-issued patent,] the level of skill in the art, or what would have been obvious to a person skilled in the art." Following this lead, the court likewise declines to issue findings of fact or conclusions of law as to defendants' claim of obviousness-type double patenting because this issue was not litigated at trial. Defendants merely made passing reference to it in their opening statement, claiming:

And then, lastly, [defendants] will show that [plaintiffs] obtained a patent that issued before the '352 patent, with claims to a method of making ripe [hGH] and that [c]laim 1 of the '352 patent is invalid for obviousness type double patenting and the '352 patent has - will have the effect of extending the amount of protection that - beyond permissible statutory term.

(D.I. 183 at 4) Defendants presented neither evidence nor expert

²²At bar, defendants argue in favor of applying the one-way test whereas plaintiffs argue in favor of applying the two-way test.

testimony on this issue. The '697 patent is the only possible evidence that the court could consider in deciding this issue. Nevertheless, the '697 was not directly entered into evidence during either the instant infringement action or the 146 action; it only became of record during the 146 action as part of the interference files provided by the United States Patent and Trademark Office. (See Bio-Technology I; DE 1009) Accordingly, the court concludes that defendants may not avail obviousness-type double patenting as a defense to invalidate the '352 patent.

D. Enforceability

a. Inequitable Conduct

69. Defendants claim that plaintiffs engaged in inequitable conduct during the "prosecution of applications leading to the '352 patent"²³ in three distinct ways. First, defendants argue that plaintiffs included Example 1 written in the past tense in the 1983 PCT application and in the 1984 U.S. application knowing that the work represented in this example had not actually been performed. Second, defendants allege that plaintiffs misrepresented the disclosure of the 1983 PCT application during the prosecution of applications leading to the

²³The parties did not specify the particular prosecution histories of the applications leading to the '352 patent in contention. Recall that the applications leading to the '352 patent include: (1) U.S. Application No. 372,692; (2) U.S. Application No. 959,856 (the "'856 application"); (3) U.S. Application No. 759,106; (4) U.S. Application No. 215,602; (5) U.S. Application No. 910,230; and (6) the 1984 U.S. application. The court assumes that defendants refer to these six applications when they state "applications leading to the '352 patent."

'352 patent. Third, defendants allege that plaintiffs did not provide the PTO with either the 1982 Danish application or an English translation thereof during the prosecution of applications leading to the '352 patent.

70. Applicants for patents and their legal representatives have a duty of candor, good faith, and honesty in their dealings with the PTO. Molins PLC v. Textron, Inc., 48 F.3d 1172, 1178 (Fed. Cir. 1995); 37 C.F.R. § 1.56(a). This duty is predicated on the fact that "a patent is an exception to the general rule against monopolies and to the right of access to a free and open market." Precision Instrument Mfg. Co. v. Auto. Maint. Mach. Co., 324 U.S. 806, 816 (1945). A breach of this duty constitutes inequitable conduct. Molins, 48 F.3d at 1178.

71. If it is established that a patent applicant engaged in inequitable conduct with respect to one claim, then the entire patent application is rendered unenforceable. Kingsdown Med. Consultants v. Hollister Inc., 863 F.2d 867, 877 (Fed. Cir. 1988). Additionally, "[a] breach of the duty of candor early in the prosecution may render unenforceable all claims which eventually issue from the same or a related application." Fox Indus., Inc. v. Structural Pres. Sys., Inc., 922 F.2d 801, 803-04 (Fed. Cir. 1991).

72. The court fully addressed all issues of defendants' inequitable conduct arguments in the 146 action. See Bio-Technology I, D.I. 100. The court will not repeat its

findings of fact and conclusions of law in the instant opinion. The court concluded that plaintiffs committed inequitable conduct, thereby rendering the '352 patent unenforceable. Id.

b. Prosecution Laches

73. Defendants argue that the '352 patent is unenforceable because it issued as a patent after an unreasonable and unexplained delay in prosecution. More specifically, defendants claim that plaintiffs did not submit claims to "biosynthetic ripe hGH" until March 10, 1995, even though it filed the 1984 U.S. application nearly ten years earlier on August 8, 1984.

74. The court declines to consider this "late filing of a claim" argument because defendants did not address this contention in any manner during either the infringement action or the 146 action. In fact, defendants did not even mention it in passing during the course of either the instant litigation or the 146 action. Likewise, defendants offered no evidence to substantiate their allegations; they rely merely on the filing dates of the 1984 U.S. application and the '352 patent.

75. Even if the court were to consider the merits of this defense, defendants fail to prove the defense of prosecution laches by clear and convincing evidence. The Federal Circuit held in Symbol Tech. v. Lemelson Med., 277 F.3d 1361 (Fed. Cir. 2002), that the equitable doctrine of laches may be applied to bar enforcement of patent claims that issued after an

unreasonable and unexplained delay in prosecution, even though the applicant complied with pertinent statutes and rules. Since neither Congress nor the Federal Circuit has provided any further guidance on the legal standard applicable to the prosecution laches defense, this court has focused the inquiry on two precepts. The initial inquiry is based on the "unreasonable and unexplained delay" rule set forth in In re Bogese, 303 F.3d 1362, 367 (Fed. Cir. 2002), with primary attention on the "reasonableness of the delay." Intuitive Surgical, Inc. v. Computer Motion, Inc., No. 01-203-SLR, 2002 WL 31833867, *3 (D. Del. Dec. 10, 2002). Second, in reviewing the record to determine whether the delay at issue was unreasonable and unexplained, the court must consider the fact that prosecution laches is an equitable tool which has been used sparingly in only the most egregious of cases. Id. There is no evidence of record to suggest that plaintiffs unreasonably delayed in filing claim 1 of the '352 patent. To the contrary, plaintiffs appear to have actively pursued the invention of claim 1 from the filing of the 1984 U.S. application through a series of five continuation applications to the application which granted as the '352 patent. The court also does not consider a ten year span from the filing of the 1984 U.S. application to the filing of the application which became the '352 patent surprising or even uncommon since the prosecution of a single application often requires significant time, on average from three to five years. Indeed,

at least one other district court has held, post-Symbol, that a delay of more than nine years between the filing of a parent application and the issuance of a continuation or divisional patent is not unreasonable. See Gen-Probe Inc. v. Vysis, Inc., No. 99-CV-2668H (S.D. Cal. Aug. 5, 2002) (holding that an eleven year delay between the filing and the issuance of a patent is not unreasonable). Moreover, this court has held that the relevant inquiry is not whether the patentee unreasonably delayed in filing specific claims in a patent application. Intuitive Surgical, 2002 WL 31833867 at *5. Rather, it is whether the patentee unreasonably delayed in prosecuting those claims once filed. Thus, the court concludes that plaintiffs did not obtain claim 1 of the '352 patent after an unreasonable and unexplained delay in prosecution. Accordingly, defendants may not rely on the doctrine of prosecution laches to render the '352 patent unenforceable.

IV. CONCLUSION

For the reasons stated, the court finds the '352 patent invalid on anticipation grounds pursuant to 35 U.S.C. 102(a). The court also finds the '352 patent unenforceable due to inequitable conduct. An order shall issue.

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

NOVO NORDISK PHARMACEUTICALS,)
INC., and NOVO NORDISK A/S,)
)
)
Plaintiffs,)
)
v.) Civ. No. 02-332-SLR
)
)
BIO-TECHNOLOGY GENERAL CORP.)
and TEVA PHARMACEUTICALS USA,)
INC.,)
)
Defendants.)

O R D E R

At Wilmington this 3rd day of August, 2004, consistent with the opinion issued this same date;

IT IS ORDERED that U.S. Patent No. 5,633,352 ("the '352 patent) is invalid under 35 U.S.C. 102(a).

IT IS FURTHER ORDERED that the '352 patent is unenforceable due to inequitable conduct.

The Clerk of Court is directed to enter judgment in favor of defendants and against plaintiffs.

Sue L. Robinson
United States District Judge