United States District Court,
D. Massachusetts.

BIOGEN, INC,
Plaintiff.
v.
BERLEX LABORATORIES, INC,
Defendant.
Berlex Laboratories, Inc,
Plaintiff.
v.
Biogen, Inc,
Defendant.
Berlex Laboratories, Inc,
Plaintiff.
v.
Biogen, Inc,
Defendant.

Nos. C.A. 96-10916-MLW, 96-12487-MLW, 98-11728-MLW

Aug. 15, 2000.

As Corrected Sept. 19, 2000.
Memorandum Supplementing Decision Sept. 19, 2000.

Parties moved for summary judgment in three consolidated cases concerning infringement of patents relating to use of recombinant DNA technology to produce human beta interferon protein in Chinese hamster ovary cells (CHO) cells for use in treatment of multiple sclerosis. The District Court, Wolf, J., held that: (1) competitor's method of introducing interferon genes and dihydrofolate reductase (DHFR) marker genes into cells on separate DNA constructs did not literally infringe patent; (2) prosecution estoppel barred claim of infringement of patent; (3) competitor's product, which achieved interferon concentration levels in the 1,200,000 to 1,600,000 IU/ml range after confluence and superinduction, did not literally infringe patent.

Judgment of noninfringement.

Court-Filed Expert Resumes

5,376,567, 5,795,779. Not Infringed.

Supplemental opinion

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WOLF**, District Judge.**

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I. SUMMARY

These three, consolidated cases concern whether Biogen, Inc. ("Biogen") infringes patents owned by Berlex Laboratories, Inc. ("Berlex"). The issues presented relate to the use of recombinant DNA technology to produce human beta interferon ("interferon" or "IFN") protein in Chinese hamster ovary cells ("CHO" cells), cells which have been adapted to grow in laboratory or manufacturing conditions. Beta interferon is used to treat multiple sclerosis. Both Avonex, which is marketed by Biogen, and Betaseron, which is marketed by Berlex, are beta interferon products which have been approved by the United States Food and Drug Administration for the treatment of multiple sclerosis.

Berlex is a New Jersey subsidiary of Schering AG, a German pharmaceutical company. Berlex is the co-assignee of the U.S. Patents No.'s 4,966,843 (the " '843 Patent"), 5,376,567 (the " '567 Patent"), and 5,795,779 (the " '779 Patent"). Biogen is a Massachusetts company that is principally engaged in the business of developing and manufacturing pharmaceutical products through genetic engineering.

Berlex alleges that in producing Avonex Biogen infringes Berlex's '567 and '779 Patents both literally and under the doctrine of equivalents. Berlex seeks damages for the past infringement which it alleges and a permanent injunction to prevent future infringement. Biogen requestsa declaratory judgment that it does not infringe the '567 or '779 Patents. Alternatively, Biogen contends that if Berlex's proposed claim construction is adopted by the court the '567 Patent is invalid because it lacks the legally required adequate written description. In addition, Biogen asserts that both the '567 and '779 Patents should not be enforced because Berlex engaged in inequitable conduct in prosecuting the applications which led to the issuance of each patent by the United States Patent and Trademark Office (the "PTO").

The parties engaged in extensive discovery for several years. At least one party has moved for summary judgment on each issue of the foregoing issues. The parties conducted two "tutorials" to educate the court on the relevant science, which is summarized in s. III A, infra.

The parties agree that there are no material disputed facts concerning whether Biogen infringes the '567 Patent either literally or under the doctrine of equivalents. They also agree that there are no disputed material facts concerning whether the '779 Patent is infringed literally. While Berlex argues that there is a genuine factual dispute concerning whether Biogen infringes the '779 Patent under the doctrine of equivalents, the court finds that this is not correct. *See* s. VII, infra. As there are no material facts genuinely in dispute, the questions concerning infringement of the '567 and '779 Patent are ripe to be resolved on the pending motions for summary judgment.

In essence, issues of claim construction are dispositive in these cases. Biogen infringes each of the claims at issue, either literally or under the doctrine of equivalents, if the claim constructions advocated by Berlex are correct. Biogen does not infringe either the '567 or '779 Patent if Biogen's proffered claim constructions are correct.

[1] Claim construction is an issue to be decided by the court. Thus, the court held a " *Markman* hearing," for the purpose of deciding how to construe the relevant claims, in connection with the hearings on the motions for summary judgment which were conducted on March 7, 8, 9, 10, and 13, 2000.

For the reasons described in detail in this Memorandum, the court concludes that Biogen's proposed construction of each of the claims at issue is correct. Thus, Biogen is entitled to summary judgment on its request for a declaratory judgment that it does not infringe either the '567 Patent or the '779 Patent. The court understands that these decisions resolve these cases, subject to possible appeal. The court is, therefore, not deciding Biogen's motions for summary judgment on the questions whether the '567 and/or '779 Patents are invalid or unenforceable.

In view of the foregoing, the parties are being ordered to confer; to inform the court, by September 8, 2000, whether they agree that final judgment should now be entered for Biogen; and if so, to submit a proposed form of judgment.

II. STANDARD FOR SUMMARY JUDGMENT

The court's discretion to grant summary judgment is governed by Fed.R.Civ.P. 56. Rule 56 provides, in pertinent part, that the court may grant summary judgment only if "the pleadings, depositions, answers to interrogatories, and admissions on file, together with the affidavits, if any, show that there is no genuine issue as to any material fact and that the moving party is entitled to judgment as a matter of law." Fed.R.Civ.P. 56(c); *see also* Karlin Tech. Inc. v. Surgical Dynamics, Inc., 177 F.3d 968, 970 (Fed.Cir.1999).

The facts must be viewed in the light most favorable to the non-moving party. Rodime PLC v. Seagate Tech., Inc., 174 F.3d 1294, 1301 (Fed.Cir.1999), *cert. denied,* 528 U.S. 1115, 120 S.Ct. 933, 145 L.Ed.2d 812 (2000). "When a party fails to make a showing sufficient to establish the existence of an element essential to that party's case, and on which that party bears the burden of proof at trial, there can no longer be a genuine issue as to any material fact ... and the moving party is entitled to judgment as a matter of law." Smith v. Stratus Computer, Inc., 40 F.3d 11, 12 (1st Cir.1994), *cert. denied,* 514 U.S. 1108, 115 S.Ct. 1958, 131 L.Ed.2d 850 (1995) (citation omitted). "[S]ummary judgment is as appropriate in a patent case as in any other." Avia Group Int'l, Inc. v. L.A. Gear Calif., Inc., 853 F.2d 1557, 1561 (Fed.Cir.1988) (citations and internal quotations omitted).

In determining the merits of a motion for summary judgment, the court is compelled to undertake two inquiries: (1) whether the factual disputes are genuine, and (2) whether any fact genuinely in dispute is material. Anderson v. Liberty Lobby, 477 U.S. 242, 247-48, 106 S.Ct. 2505, 91 L.Ed.2d 202 (1986). "As to materiality, the substantive law will identify which facts are material. Only disputes over facts that might affect the outcome of the suit under the governing law will properly preclude the entry of summary judgment." *Id.* To determine if the dispute about a material fact is "genuine," the court must decide whether "the evidence is such that a reasonable [factfinder] could return a verdict for the nonmoving party." *Id.*

III. FACTS

A. *Technical Background*

The relevant facts, which unless otherwise noted are not in genuine dispute, include those set forth below. The history of events relating to this litigation is described chronologically in this section of this Memorandum to place them in context. At the risk of redundancy, the salient facts are repeated, and in some

instances amplified, in the following sections which analyze each of the motions for summary judgment being decided.

Using recombinant DNA technology, proteins such as interferon can be produced in "host" cells which normally do not produce those proteins. Foreign DNA FN1 encoding the interferon protein is introduced into the host cell on a "DNA construct," which is also sometimes referred to as a "plasmid" or "vector." A DNA construct is an engineered piece of DNA that serves as a vehicle to facilitate transfer of a gene into the host cell. Once introduced into a eukaryotic cell FN2, the DNA construct may integrate into the chromosome FN3 of the host cell. If stably integrated, the "gene of interest," in this case the interferon gene, can be "transcribed" FN4 into "RNA." FN5 That RNA may be "translated" FN6 into protein by the host cell. If the process is successful, progeny of the host cell will also have the gene of interest and produce the protein.

FN1. "DNA" is an abbreviation for Deoxyribonucleic acid, a double-stranded, helical molecule composed of four different types of "nucleotides," the order of which determines the genetic code for the synthesis of proteins.

FN2. Eukaryotic cells contain nuclei, as distinguished from prokaryotic cells, such as bacteria, which have no nuclei.

FN3. A chromosome is the genetic material of a cell, made primarily of DNA, which contains the genes that encode the information necessary for the production of proteins. A gene is a discrete sequence of DNA that encodes a protein.

FN4. Transcription is the process of reading the nucleotide sequence of a gene and constructing messenger RNA encoding that sequence.

FN5. RNA is an abbreviation for Ribonucleic acid, a single-stranded nucleic acid which carries genetic messages from the nucleus to the cytoplasm where it is translated into protein.

FN6. Translation is the process of creating a protein from an RNA sequence.

The process of introducing a foreign gene into a cell is known as "transfection." The term "transform" is often used interchangeably with "transfect," although "transform" implies that the foreign DNA has been successfully incorporated in the host cell. In this Memorandum the terms "transform" and "transformation" refer to the successful introduction of foreign genes into the chromosome of a host cell.

Multiple genes can be introduced into a host cell simultaneously, in a process called "co-transformation." Co-transformation is valuable because successful transformation is a rare event. Typically less than one cell in 100,000 successfully integrates a foreign gene. Thus, identification of CHO cells transformed with the interferon gene is both difficult and important.

To facilitate detection of transformed cells, scientists can introduce a "selectable marker gene," as well as the gene of interest, into a host cell. A selectable marker gene encodes a protein required by the cell to survive in certain growth conditions. Cells lacking this marker gene are used as hosts. After transformation has been attempted, scientists place the cells in medium which is nutritionally deficient or toxic to cells which did not integrate the marker gene and, therefore, do not produce the protein it encodes. A cell which has been transformed to include the selectable marker gene will survive in this medium because the transformed cell will compensate for the nutritional deficiency or toxicity. A cell which has not been transformed will die. In essence, the cells which have been transformed to contain the selectable marker gene will live and be identifiable as transformed.

When co-transformation is attempted, if the selectable marker gene has been successfully introduced, the interferon gene may have been successfully introduced as well. Thus, the marker gene facilitates the identification of cells that have been transformed to include interferon.

Co-transformation can be attempted by placing two genes on a single DNA construct and introducing it into the cell. This is called "linked co-transformation," or co-transformation with a "single construct". *See* Exhibit A hereto. Alternatively, co-transformation can be attempted by placing two genes on different DNA constructs, and simultaneously introducing them into the cell. *Id*. This is referred to as "unlinked co-transformation" or co-transformation employing "multiple constructs". *See* Exhibit B hereto. Berlex uses a single construct to introduce interferon and marker genes into CHO host cells. Biogen employs multiple constructs to accomplish this. The legal implications of this difference are at the heart of the instant litigation.

After either linked or unlinked co-transformation is accomplished, the host cell is grown in a "culture medium" in order to allow the gene of interest, in this case interferon, to be expressed as a protein. A "culture medium" is a solution that contains the nutrients required for maintenance and growth of the cell. When monolayer cultures, which are cultures that are grown on the surface of a plate or roller bottle with a layer one cell thick, are used, the monolayers can be grown to "confluency." "Confluency" is the point at which the cells touch each other, and thus reach the maximum density of the cells in that medium.

To stimulate the production of the maximum amount of interferon, the transformed cells may be "superinduced." "Superinduction" involves treating the transformed cells with certain toxic chemicals which induces production of a high level of interferon, but ultimately kill the host cells.

The concentration of interferon in a medium is typically measured by International Units per milliliter. This is abbreviated as "IU/ml."

After superinduction, the interferon produced is harvested. It is then available for use in products such as Avonex and Betaseron.

B. *The Axel Patents Licensed by Biogen*

In 1979, Drs. Richard Axel, Michael Wigler, and Saul Silverstein published an article in the journal *Cell* disclosing the unlinked co-transformation procedure. *See* M. Wigler, *et al.,* "Transformation of Mammalian Cells with Genes from Procaryotes and Eucaryotes," 16 *Cell* 777 (1979), Affidavit of David B. Bassett in Supp. of Biogen, Inc.'s Mots. for Summ. J. ("Bassett Aff.") Ex. 26, at BG0029574. Among other things, the

authors wrote that: "This paper demonstrates the feasibility of co-transforming cells with two physically unlinked genes. Co-transformed cells can be identified and isolated when one of these genes codes for a selectable marker." *Id*.

In 1980, Drs. Axel, Wigler, Silverstein, and others published another article discussing linked co-transformation. *See* M. Wigler, *et al*., "Transformation of Mammalian Cells With an Amplifiable Dominant-Acting Gene," 77 *Proc*. *Natl Acad*. *Sci*. 6:3567, 3569 (1980), Bassett Aff. Ex. 31.

Drs. Axel, Wigler, and Silverstein were granted patents, two of which (the Axel '216 and '665 Patents) are prior art to Berlex's patents. The initial patent describes experiments using both linked and unlinked co-transformation. U.S. Patent No. 4,399,216, (the Axel " '216 Patent") at 2:32-35, 5:3-6, 5:24-28, 5:63-68, 6:62-66, 7:27-31, 8:36-44,FN7 Bassett Aff. Ex. 8. The experiments also identify interferon as the gene of interest, DHFR FN8 as a selectable marker gene, and CHO cells as host cells. Id. The application for this patent was filed on February 25, 1980, and the patent issued on August 16, 1983. Id. at BG0017365. A subsequent Axel patent, deriving from the same application, claims a "Chinese Hamster Ovary cell ... wherein the proteinaceous material is interferon protein...." U.S. Patent No. 5,179,017 (the "Axel '017 Patent"), at 42:49-51, Bassett Aff. Ex. 9. In addition, the inventors were issued an International patent with a specification which was identical to that of the '216 and '017 Patents. International Patent Application No. PCT/US81/00240 published Sept. 3, 1981 (the "Axel International Patent"); Letter from W.F. Lee and R.W. Clary to Judge Wolf (Aug. 10, 2000). The Axel '216 Patent, the Axel '017 Patent, and the Axel International Patent are sometimes referred to as the "Axel Patents."

FN7. Citations to patents will contain references to the column number and line number in the column in which the cited text appears. The first number refers to the column number; the number following the colon refers to the line number within that column.

FN8. DHFR is an abbreviation for Dihydrofolate reductase, an enzyme which is commonly used as a selectable marker in recombinant DNA technology.

Biogen has a license from Columbia University, the assignee of the Axel Patents, to produce interferon by using *unlinked* co-transformation and CHO cells in its production of Avonex.

As indicated earlier, the parties dispute whether Berlex's patents, which are described below, are limited to the use of linked co-transformation-the expression of human interferon in CHO cells transformed by employing a single DNA construct comprising multiple genes-or whether it is broader and also encompasses unlinked co-transformation where interferon and marker genes are inserted into a host cell as parts of two distinct DNA constructs.

C. *The Berlex Patents*

As also indicated earlier, Berlex owns three patents pertinent to this litigation. The '843 Patent issued on October 30, 1990. '843 Patent, Bassett Aff. Ex. 1, at BG0035689. It is literally restricted to the use of a single DNA construct comprising both interferon and marker genes to express human interferon in CHO cells. Id. Berlex has not sued Biogen for infringement of the '843 Patent.

The '567 Patent, entitled "Expression of Interferon Genes in Chinese Hamster Ovary Cells," was issued to Berlex on December 27, 1994, based upon a continuation application filed in the '843 Patent prosecution. '567 Patent, Bassett Aff. Ex. 2. Berlex asserts that the claims of the '567 Patent claims fall into three distinct categories, which it characterizes as: (a) construct claims; (b) cell claims; and (c) method claims. Biogen contends that all of the claims of the '567 Patent are limited to the use of a single construct.

The claims Berlex characterizes as the construct claims of the '567 Patent (Claims 1, 2-9, 15-21, 40, 41, and 90) explicitly recite a single DNA construct containing both interferon and DHFR genes as the means of transforming CHO cells. '567 Patent, Bassett Aff. Ex. 2, 27-32. Berlex does not allege that Biogen literally infringes these claims, but argues instead that Biogen infringes them under the doctrine of equivalents.

The claims Berlex characterizes as cell claims (Claims 10-13, 36-39, 66-69) pertain to CHO cells which have been transformed with human interferon. The broadest of these cell claims, Claims 66-69, describe CHO cells "having incorporated therein an expressible gene encoding human (alpha)-or (beta)-interferon," without reciting any specific construct configuration for achieving transformation. Id. at 30:37-39. Berlex contends that Biogen literally infringes claims 66-69.

Claims 10-13 and 36-39, describe CHO cells having incorporated into their chromosomes a single DNA construct bearing both interferon and marker genes. Id. at 27:49-63; 28:61-29:3. Berlex charges Biogen with infringing these claims under the doctrine of equivalents.

Claims 42 and 70 are the broadest of the claims that Berlex characterizes as method claims. They describe methods of interferon production in CHO cells, without specifying the use of a single DNA construct comprising an interferon gene and a marker gene. Id. at 29:18-24 (Claim 42), 30:49-55 (Claim 70). Berlex asserts that Biogen literally infringes these and similar or dependent claims (Claims 42-45, 52, 56, 58, 64, 70, 72, and 78).

D. *The* '779 Patent

This litigation commenced in May 1996. In March 1998, Berlex submitted to the PTO claims which emerged as the '779 Patent. The '779 Patent is entitled "Human Interferon-(beta) (IFN-(beta)) Produced in Chinese Hamster Ovary (CHO) Cells." It was issued to Berlex on August 18, 1998. '779 Patent, Bassett Aff. Ex. 3. All claims of the '779 Patent expressly require a cell culture composition directly resulting from the secretion of interferon from transformed CHO cells with an interferon concentration of between 150,000-600,000 IU/ml. Id. at 28:6-30:19.

Berlex contends that Biogen literally infringes Claim 1 and representative dependent claims (Claims 2, 8, 9, 11, 12, 21, 25, 26, and 37) of the '779 Patent because Biogen's product passes through the 150,000-600,000 IU/ml range before achieving concentrations of 1,200,000-1,600,000 IU/ml. Alternatively, Berlex contends that Biogen infringes the '779 Patent under the doctrine of equivalents.

E. *The Prosecution of the Berlex Patents*

1. *The 1982 Application*

On November 1, 1982, Drs. Francis P. McCormick, Michael A. Innis, and Gordon M. Ringold (the "inventors" or the "applicants") filed with the PTO U.S. Patent Application No. 06/438,991 (the "1982 application"), entitled "Expression of Interferon Genes in Animal Cells." Bassett Aff. Ex. 4, at 5. Dr.

Ringold has testified in this case that he was aware of, and had performed, unlinked co-transformation prior to the collaboration with Drs. McCormick and Innis which produced the Berlex patents. Deposition of Gordon M. Ringold ("Ringold Dep."), Battin Decl. Ex. 15, at 68-69. In fact, the work underlying the original application was based on the hypothesis that linked co-transformation would increase the frequency of successful co-transformation. Id. at 65, 588. Dr. Ringold believed that linked co-transformationdistinguished his work from what he understood to be Axel's unlinked co-transformation procedure. Id.

The claims of the original 1982 application expressly required a single DNA construct containing: (1) a replication sequence; (2) a selectable marker sequence; and (3) an interferon gene for expression of interferon in mammalian cells. Bassett Aff. Ex. 4, at 23. The original claims did not expressly require a "linkage" of those three elements. Id.

2. *The 1984 Amendments*

In May 1984, the Examiner rejected the pending claims as anticipated and obvious in light of the prior art. Id. at 45-48. In order to avoid the prior art, on September 14, 1984, the inventors amended the claims to require a linkage of the three elements. Id. at 75-77. It was this linkage of the selectable marker and IFN on the same DNA construct which the inventors claimed led to the "unexpected," positive results of their invention. Id. at 82.

More specifically, the inventors claimed that the linkage of the interferon gene and selectable marker gene on a single DNA construct solved problems of human interferon toxicity to CHO cells, and the contamination of human interferon with hamster interferon. They wrote to the PTO that:

applicants' invention resides in the construction of a plasmid which, when introduced into CHO cells which are selected and grown so as to express interferon, produces human interferon in large quantities and to the exclusion of any hamster interferon [citation omitted]. It was well known at the time of filing this application that human interferon is toxic to animal cells so that it inhibits cell growth as it is produced.... Thus, it was completely unexpected that the CHO cells did not die as the human interferon was being produced.... Furthermore, it was well known that mammalian host cells produced mixtures of animal and human IFN when transformed with a recombinant DNA containing a human interferon gene. Therefore, it was unexpected that *only* human interferon was produced by the CHO cells....

Id. at 81-82 (emphasis in original). High levels of expression of human interferon without hamster interferon and without human interferon toxicity to CHO cells was the unexpected result according to the inventors. Id.

The inventors asserted that this result was due to the linkage of the interferon gene and the selectable marker gene on a single DNA construct. They stated that:

These unexpected and advantageous results were accomplished by linking the interferon gene with the gene containing the selectable marker on a *single* DNA construct so that coamplification of the genes occurred. In the prior art co-transformation was generally used, wherein two plasmids with the separate genes were cotransformed into the host. Thus, the instant DNA construct differs from what was done previously, and the results obtained on transforming the host with this construct were totally surprising.

Id. at 82 (emphasis in original).

As the foregoing statement reflects, the applicants distinguished the Axel patent on the basis of their single DNA construct configuration and the linkage of the interferon gene and the marker gene on that construct. They went on to emphasize this point, stating that the Axel process:

involves *co-transformation* where two separate DNA constructs with *unlinked* genes are integrated into the plasmid. In contrast, applicants' process deals with *coamplification* where the interferon gene and selectable marker gene are *linked* on the same DNA construct.

Id. at 83 (emphasis in original).FN9

FN9. This statement was factually inaccurate. In fact, Axel disclosed both linked and unlinked co-transformation. *See* Axel '216 Patent, Bassett Aff. Ex. 8. This statement was made in September 1984, more than a year after the Axel patent issued. The parties do not now dispute that Axel disclosed both methods of co-transformation. Mem. of Biogen, Inc. in Supp. of Mot. for Summ. J. of Invalidity ("Bg. Invalidity Mem.") at 17 n. 10; Mem. of Law in Supp. of Berlex's Mot. for Summ. J. of Literal Infringement ("Blx.Lit.Infr.Mem.") at 27.

3. *The 1985 CIP Application*

On July 31, 1985, Cetus Corporation, the original assignee of the '843 Patent, filed a continuation-in-part (CIP) application. The text of this application is the specification of both of Berlex's patents at issue in this case. The 1985 CIP application was entitled "Expression of Interferon Genes in Chinese Hamster Ovary Cells." 1985 CIP, Bassett Aff. Ex. 5, at 5. All claims of the 1985 CIP application expressly recited a single, three part DNA construct including both interferon and marker genes. Id. at 46:2-49:17. All of the experimental examples describe CHO cells that had been transformed with a single DNA construct. Id. at 29:14-44:4. None of the examples describe transformation utilizing separate constructs. Id.

The Background of Invention generally describes the use of interferons as therapeutic agents, and the efficacy of expressing IFN in bacterial cells, using recombinant DNA technology. Id. at 5:4-7:10. It refers to the Axel International Patent, which it said, "broadly describes processes for inserting DNA into eukaryotic cells and for producing proteinaceous material, but provides no enabling details regarding suitable DNA fragments, hosts, transforming vectors, methods for transformation, promoter and control sequences which facilitate expression, *and other essential components*." Id. at 7:2-7 (emphasis added). The applicants thus deemed not only "hosts" but also "suitable DNA fragments," "transforming vectors," and "methods for transformation" as "essential components" for enabling interferon expression.

The CIP application added to the specification a new Summary of Invention section. The Summary of Invention explicitly describes a single DNA construct with an operable linkage of several genes as being the invention. It states:

[T]he present invention provides *a DNA construct* for the expression of the human interferon gene in Chinese hamster ovary cells or progeny thereof *comprising an operable linkage of:*

(a) a nucleotide sequence from a cloning vector which allows for replication in a prokaryotic cell;

(b) a first gene capable of transcription and translation in Chinese hamster ovary cells or progeny thereof operably linked to a selectable marker for the selection of Chinese hamster ovary (CHO) cell transformants or progeny thereof; and

(c) a human interferon gene capable of transcription and translation in Chinese hamster ovary cells or progeny thereof.

Id. at 7:12-22 (emphasis added).

"[O]ther aspects" of the invention were similarly described as requiring the use of the single construct comprising both genes. The Summary states: "In other aspects, the invention provides for transforming vectors carrying *the DNA construct,* suitable CHO hosts transformed with the cloning vector, and expression control sequences for expressing the DNA fragments." Id. at 7:23-26 (emphasis added). The Summary of Invention also describes a method of producing IFN in CHO cells comprising "introducing into a Chinese hamster ovary cell or progeny thereof *the above-described DNA construct*." Id. at 7:29-30 (emphasis added).

Thus, in the Summary the applicants described their invention as the single, three-part DNA construct. The DNA constructis never characterized as possessing fewer than three elements. The Summary does not describe the invention as the expression of interferon in CHO cells generally. Indeed, Berlex agrees that the foregoing passages in the summary describe a single construct. Mar. 7, 2000 Tr. at 68. The Summary concludes:

In preferred embodiments, DNA fragments which code for one or more IFNs are isolated from appropriate human cells; introduced into CHO cells by DNA transfection, or by penetration of viral vectors carrying the DNA fragment, or by transfection of cloned plasmids into cells that express T-antigens; and expressed by the host cells; and the expressed product is isolated and purified.

Id. at 8:11-16.

Four figures in the specification represent DNA constructs used for the expression of IFN in CHO cells. Figs. 1-4, Id. at 52-53. Each of these figures depicts interferon and marker genes operably linked on a single DNA construct. Id. at 52-53, 8:18-26. No drawing depicts a marker gene on one vector, and an interferon gene on another vector. Id.

The 1985 application also added a definition of "operable linkage" to the Description of the Preferred Embodiments. It said:

The term "operably linked" or "operable linkage" as used herein regarding DNA sequences or genes refers to the situation wherein the sequences or genes are juxtaposed in such a manner so as to permit their ordinary functionality. For example, a promoter operably linked to a coding sequence refers to those linkages where the promoter is capable of controlling the expression of the sequence. The sequence operably linked to a selectable marker has the same significance: i.e., it permits the selectable marker to be positioned in the transcript so as to participate in the selection procedure after the sequence has been expressed in the host. Similarly, an *operable linkage of sequences and genes signifies that the sequences and genes are so positioned in a DNA construct* as to permit expression of the sequences in the desired manner.

Id. at 11:21-33 (emphasis added). Thus, the inventors tied the concept of operable linkage to the use of a single DNA construct. Id.

The Description of the Preferred Embodiments defines the term "DNA construct" as "any suitable cloning vector, including, for example, plasmids, viruses such as SV40, polyoma virus, bovine papilloma virus, mouse mammary virus and the like, and bacteriophages." Id. at 12:6-9. The Description continues:

The method of effecting expression of heterologous genes in CHO host cells or progeny thereof generally involves preparing DNA constructs as defined above operably linked to a nucleotide sequence for replicating in a prokaryotic cell, preferably *E. coli;* a marker gene operably linked to a CHO cell selectable marker for the selection of transformants or progeny thereof, and operably linked to a promoter and start and stop codons; and an interferon gene from a human source, operably linked to an endogenous or heterologous promoter and translation sequences (start and stop codons) for expression of the interferon gene in CHO cells or progeny thereof. *This DNA construct* is then introduced in CHO cells or progeny thereof, preferably in a culture, by any technique, including any of the three techniques described below, the transformed cells are selected and then grown under selective conditions whereby the interferon gene is expressed; and the interferon so produced is isolated and purified.

Id. at 12:33-13:13 (emphasis added). Later, the Description states: "In accordance with the present invention, any approach may be used to introduce the cloned DNA into CHO cells and to select and grow the transformed cells for expression of the protein. Among the approaches for transfection are the following three approaches": (1) transfection, where foreign DNA is precipitated from solution and enters cells in this insoluble form; (2) introduction of DNA through a virus which can penetrate the cell membrane; and (3) transfection of cloned plasmids into cells that express SV40 regulatory proteins (T-antigens). Id. at 27:7-28:16. Dr. John Hiscott, one of Berlex's experts, has opined that viral transfection "would not be expected to involve use of a selectable marker gene." Rebuttal Expert Report of Dr. John Hiscott ("Hiscott Reb. Rpt."), Decl. of Jennifer L. Gillum ("Gillum Decl."), Ex. 2, at 51. However, Dr. Hiscott does not assert that transfection with a virus could not employ a selectable marker. Moreover, counsel for Berlex acknowledged at oral argument that the above quoted language at columns 27 and 28 is "inconsisten[t]" with the language appearing in columns 12 and 13, which states that "[t]his DNA construct" is introduced into the cells according to one of these three approaches. Mar. 7, 2000 Tr. at 76.

The Description of Preferred Embodiments also emphasizes the use of CHO cells. It states:

Chinese hamster ovary cells or progeny thereof are used as the host cells herein. They do not coproduce endogenous (hamster) IFN constitutively or by induction, whether a promoter endogenous to IFN or a heterologous promoter for IFN is employed, in contrast to other eukaryotic hosts such as mouse cells. Furthermore, CHO cells are largely resistant to the anti-cellular activity of the human IFNs produced. When CHO cells are transformed with IFN gene under its own promoter control, expression levels for IFN are high for induction and low for constitutive production. With heterologous promoters, no detectable induction is observed, but only constitutive production of IFN.

1985 CIP, Bassett Aff. Ex. 5, at 12:22-32. CHO cells facilitated the recombinant expression of human interferon without contamination from the endogenous host.

The Description of the Preferred Embodiments identifies the potential use of various cloning vectors,

selectable marker genes, and promoters. Id. at 13:14-30; 26:24-32. It does not state however, that the singular DNA configuration is not critical to the invention, and does not identify any alternative to using a single construct. Indeed, the specification never suggests the use of multiple DNA constructs or constructs comprising fewer than three elements.

The specification concludes:

The foregoing description of the preferred embodiments of the instant invention have been presented for purposes of illustration and description. It is not intended to be exhaustive or to limit the invention to the precise forms disclosed, and obviously many modifications and variations are possible in the light of the above teaching.

Id. at 45:4-9.

Finally, the Abstract describes the disclosed invention as single DNA constructs bearing both interferon and marker genes operably linked for the expression of human interferon in CHO cells. Id. at 50. It summarizes the disclosure as follows:

DNA constructs are prepared which operably link human interferon genes, selective, eukaryotic marker genes, and promoter and expression control sequences for the expression of human interferon in Chinese hamster ovary (CHO) cells or progeny thereof.

Id.

In an Amendment and Response under 37 C.F.R. s. 1.111 submitted on May 18, 1988, the inventors distinguished prior art on the ground that the prior art "does not disclose the coamplification and expression of linked structural or selectable marker genes." Id. at 87, 89, 91. In Remarks filed with the amendment, the applicants represented that:

The present invention is *a DNA construct* for human interferon gene expression and a method for producing human interferon from Chinese Hamster Ovary (CHO) cells. *The DNA construct* comprises: a nucleotide sequence from a cloning vector which permits replication in prokaryotes, a gene that is capable of transcription and translation in CHO cells operably linked to a marker which is capable of selecting CHO transformants, and a human interferon gene that is capable of transcription and translation in CHO cells.

Id. at 88 (emphasis added).

On August 12, 1988, the Examiner withdrew his rejections to the 1982 Application based on prior art. Bassett Aff. Ex. 4, at 205. Ultimately, on October 30, 1990, the CIP Application issued as the '843 Patent. '843 Patent, Bassett Aff. Ex. 1, at BG0035689.

Consistent with the limited disclosure of the application, it is undisputed that all of the claims of the '843 Patent are literally restricted to the use of a single DNA construct comprising both interferon and marker genes. Id. at 28:1-30:11; Blx. Tech. Mem. at 24. Berlex does not claim that Biogen infringes the '843 Patent.

4. *The 1990 Divisional Application*

On June 29, 1990, Cetus filed a divisional application, Application No. 07/546,519. Bassett Aff. Ex. 6, at 9. Although it was eventually abandoned, both the '567 and '779 Patents descend from this application. Blx. Invalidity Opp. at 12. This application characterized the disclosure as a single, three-part DNA construct. It stated: "The present invention provides a method for producing human interferon in Chinese hamster ovary (CHO) cells or progeny thereof. A DNA construct is made comprising" a replication sequence, a selectable marker gene, and an interferon gene. Bassett Aff. Ex. 6, at 114.

5. *The 1992 Preliminary Amendment*

Berlex acquired rights to the '843 Patent in 1991, and assumed control of the pending divisional patent application. Robert Chaoora Dep., Bassett Aff. Ex. 21, at 53-54; Cetus-Berlex Technology Ownership and Royalty Agreement, Bassett Aff. Ex. 18. On April 30, 1992, Berlex filed a preliminary amendment, adding new claims which Berlex contends are not limited to linked co-transformation involving a single DNA construct that includes both an interferon and a marker gene. For example, new claim 29 recited:

A DNA construct for expression in a Chinese hamster ovary cell or progeny thereof comprising a human interferon gene, said construct being *effective for transcription and translation* of said gene when *introduced into* a Chinese hamster ovary cell or progeny thereof.

Bassett Aff. Ex. 6, at 156 (emphasis added). Claim 51 described:

A method for the production of human interferon or a mutein thereof in a Chinese hamster ovary cell or progeny thereof comprising:

(a) introducing into a Chinese hamster ovary cell or progeny thereof a DNA construct for expression in a Chinese hamster ovary cell or progeny thereof comprising a human interferon gene or a gene coding for a mutein of human interferon which retains the biological activity of said interferon, said construct being *effective for transcription and translation* of said gene when *introduced into* a Chinese hamster ovary cell or progeny thereof;

(b) selecting a resultant transformed cell; and

(c) growing a selected transformant under conditions whereby the interferon gene in said construct is expressed.

Id. at 158 (emphasis added). Claim 103 recited: "A Chinese hamster ovary cell or a progeny thereof *having incorporated into* its chromosome a DNA construct of claim 30." Id. at 163 (emphasis added). As Berlex emphasizes, none of the claims recites a marker gene, and none explicitly requires the use of a single DNA construct that includes both an interferon and a marker gene.

Berlex asserted to the PTO that these claims were "different" than the single construct claims of the '843 Patent. Notably, Berlex did not state that the claims were "broader." More specifically, Berlex wrote the PTO that:

The foregoing claims are being added to cure an inadvertent oversight during ancestor prosecution leading to U.S. Patent 4,966,843.... it is noted that all claims of this application are of a scope different from that of each claim of '843.

The oversight cured above involves the unnecessary language in the '843 claims concerning prokaryotic cell nucleotide sequences and selectable marker-related sequences. Whereas such sequences are useful in various cloning experiments and procedures, they clearly are not necessary to a prime aspect of '843, i.e., "production in Chinese hamster ovary cells" (page 1, line 9). Since the prior art in the parent makes clear the nonobviousness of the combination of an expressible heterologous gene operably incorporated into Chinese hamster ovary cells, it is important that the claims reflect this nonobvious scope. Otherwise, infringers might attempt to avoid the literal scope of the claims, e.g., by simply preparing and/or using DNA constructs which omit components unnecessary for patentability and/or practical expression after selection of a favorable cell line is effected.

Id. at 164.

[2] On October 5, 1992, the Examiner rejected these new claims as unpatentable in light of the '843 Patent, under the doctrine of obviousness-type double patenting. Id. at 173, 175.FN10 The Examiner stated:

FN10. "Obviousness-type double patenting is a judge-made doctrine that prevents an extension of the patent right beyond the statutory time limit. It requires rejection of an application claim when the claimed subject matter is not patentably distinct from the subject matter claimed in a commonly owned patent." In re Berg, 140 F.3d 1428, 1431 (Fed.Cir.1998).

Although the conflicting claims are not identical, they are not patentably distinct from each other. In the parent patent, the c[la]ims recite the DNA construct by listing each element of the vector construct. The instant application seeks to remove the detailed language of the construct elements, and replaces it with functional language. This functional language effectively limits the claims to the vector construct of the '843 application. *The DNA construct, either described by its physical elements or by its function, is the same in the prior patent and the instant application*. Therefore, it would be obvious from the patent, which describes the functional characteristics of the vector in the specification, to arrive at the vector claimed in the instant application.
Id. at 175-76 (emphasis added). The functional language referenced by the Examiner included phrases such as "effective for transcription and translation," "introduced into," and "having incorporated into." Thus, as interpreted by the Examiner, requiring the DNA construct to have the function of being effective for the production of interferon was equivalent to requiring the structure described in the '843 Patent: a single DNA construct that included both an interferon gene and a marker gene.
Berlex did not dispute the Examiner's assessment. Rather, on April 16, 1993, in an effort to avoid the Examiner's rejection, Berlex filed a "terminal disclaimer," attempting to cause the '567 Patent to expire when the '843 Patent was due to expire. Id. at 185.

Following the filing of the terminal disclaimer, on October 19, 1993, the Examiner held claims 29 through 46 (all of what Berlex calls the "construct claims" then pending which did not reference "muteins") allowable over the prior art, and rejected claims 47 through 109 (the so called "method" and "cell" claims, and construct claims requiring muteins). Id. at 193-95.

At an interview between the Examiner and Berlex's attorneys on September 14, 1994, Berlex voluntarily agreed to narrow the DNA construct claims explicitly to recite a DHFR gene, even though most of the construct claims had been found allowable without such narrowing. Id. at 200, Anthony Zelano Dep.

("Zelano Dep."), Second Decl. of Richard W. Clary ("2d Clary Decl.") Ex. 6, at 212. The Examiner's Interview Summary Record memorializing the agreement states that, "Construct claims will be narrowed to include DHFR marker." Bassett Aff. Ex. 6, at 200. Initially, she wrote only that "claims will be narrowed." At Berlex's request she added the words "construct" and "to include DHFR marker."

6. *The 1994 Amendments*

On September 21, 1994, Berlex filed an Amendment narrowing all of the claims reciting a single construct which had previously been allowed to recite also the presence of a DHFR marker gene. Id. The remaining claims were modified to eliminate all reference to "muteins," but continued not to require explicitly a marker gene. Id. Berlex also added 39 claims, some of which did not recite the use of a single DNA construct. Id. at 208-11.

Each of these so called cell and method claims did not refer expressly to the single DNA construct limitation, but included language such as "having incorporated therein," "effective for expression," and "under conditions whereby the interferon gene in said construct is expressed." Id. at 205 (Claim 42). This was functional language described by the Examiner two years earlier as equivalent to the structural language describing the single, three-part DNA construct of the '843 Patent. *See, e.g.,* Id. at 175; '567 Patent, Bassett Aff. Ex. 2, at 29:21-25 (Claim 42).

In the remarks accompanying the September 21, 1994 amendment, Berlex stated that "[t]he claims continue to reflect the pioneering invention of the first expression of interferon (IFN) genes in Chinese hamster ovary (CHO) cells." Bassett Aff. Ex. 6, at 213; *see also* id. at 217-18. Noting that all references to muteins had been eliminated, Berlex stated that: "the remaining breadth of the claims, including broad method claims, such as 51 and 71, and CHO cell claims, such as 104 and 108, has essentially already been found allowable." Id. at 214.

Berlex also noted that "[p]atentability and breadth of *the current claims* reflect the non-obviousness of the first expression of human IFN in CHO cells and do not depend on any particular nucleic acid construct configuration." Id. at 223 (emphasis added). In making this statement, Berlex was evidently attempting to persuade the Examiner that previous attempts to distinguish Axel's work and patents based on the erroneous assertion that Axel disclosed only unlinked transformation were unnecessary. Rather, Berlex stated: "It is not relevant whether the Axel et al. prior art patent disclosures of record actually employ only unlinked co-transformed genes in their work. (Axel et al. do generically disclose linked such genes. See, e.g., column 7, lines 3-31, of, e.g., U.S. Patent No. 4,399,216.)" Id. While asserting that interferon expression did not depend on "any particular nucleic acid construct configuration," Berlex did not state that it did not depend on a single construct.

On November 16, 1994, the Examiner listed all of the claims being allowed. Id. at 336. The Examiner wrote, in the "Reasons for Allowance":

Applicants['] claims are directed to a DNA construct comprising a vector, an interferon gene, and a dhfr marker gene. The construct is expressed in CHO cells. The instant claims are similar to the claims in parent Patent 4,966,843 ('843), however *the instant claims recite the marker gene to be dhfr, whereas the '843 claims do not*. Since a terminal disclaimer has been filed over the '843 claims, the instant claims are held allowable.

Id. at 336 (emphasis added). Significantly, the Examiner referred to "[a]pplicants[']claims," which encompassed all of what Berlex calls its construct, cell, and method claims. She did not limit this statement only to Berlex's construct claims.

On November 25, 1994, Berlex responded to the Examiner's statement. In its "Comments on Statement of Reasons for Allowance," Berlex wrote that "as is factually clear from the involved texts of record, the claims of both this application and '843 reflect aspects other than those mentioned by the examiner, e.g., for this application, *methods and cells,* no need for a prokaryotic sequence, etc...." Brooks Decl. Ex. 23, at MW0001135 (emphasis added). This statement indicates that Berlex recognized that the Examiner's Reasons for Allowance seemed to limit the '567 Patent to a single construct using DHFR as the marker gene. Berlex evidently wished to reassert a broader interpretation.

Berlex's November 25, 1994 comments, however, are not included in the file history of the '567 Patent which is in the record in this case. *See* Bassett Aff. Ex. 6. Although the PTO received the comments, Brooks Decl. Ex. 23, at MW0001137, they do not appear in the certified copies of the file wrapper made available to the public by the PTO. Mar. 8, 2000 Tr. at 18. Thus, the public would not have had notice of Berlex's position.

7. *The 1994 Application Leading to* the '779 Patent

On August 12, 1994, Berlex filed the application, based on the specification for the '843 and '567 Patents, which culminated in the '779 Patent. Bassett Aff. Ex. 7, at 1. As indicated earlier, in May 1996, the instant litigation was commenced. On October 28, 1996, the pending claims were rejected as obvious over prior art, including the Axel '216 Patent. Id. at 112, 115-16. On March 27, 1997, about nine months after the inception of this litigation, Berlex canceled all of its pending claims and added new claims, which it characterized as "composition" or "product claims." The new claims covered a cell culture composition resulting directly from the secretion of interferon from transformed CHO cells, in which the amount of interferon is 150,000 to 600,000 IU/ml of medium. Id. at 121-25.

In its Remarks in support of the new claims, Berlex stated that "[t]he values recited in the claims are in reference to the bioassay for antiviral activity described in Table 1 of the application." These values are measurable from samples removed at any time from the claimed culture composition. Id. at 216. A copy of Table 1 is attached as Exhibit C hereto.

Table 1 disclosed only one instance in which a cell composition with an interferon level as high as 150,000-600,000 IU/ml was achieved. Bassett Aff. Ex. 3; Ex. C hereto. The Table explicitly explains that level was achieved after the transformed CHO cells had been grown to confluence and superinduction had been employed to stimulate the production of interferon. *Id.,* n. 3.

Berlex also stated in support of its new claims that:

[T]he achievement by this invention of amounts of (beta)-interferon as high as 600,000 IU/ml is strikingly superior and unexpected.... There is nothing in any of the prior art which would lead a skilled worker to have expected this result.

... The only reason applicants have chosen to place an upper limit on the literal scope is to enhance a fast allowance by minimizing potential issues. In fact, a claim scope which literally includes values higher than

600,000 IU/ml, is clearly justified.... As for the lower limit, in view of the Paragraph No. 9[of] the accompanying declaration by Dr. Jan Vilcek, it can be seen that the value of 150,000 IU is although precise, somewhat arbitrary. Thus, a scope of equivalents less than this value is warranted.

Id. at 129-30.

In his declaration submitted to the PTO pursuant to 37 C.F.R. s. 1.132, Dr. Vilcek stated that:

I know that as of November 1, 1982 the amounts of human fibroblast IFN obtained from animal cell cultures under conditions optimized for the achievement of maximal yields were generally from 10,000 to 50,000 IU/ml.... The highest amount of human fibroblast IFN produced in any animal cell system at that time that I know about, including from human fibroblast cell strains and from mammalian recombinant systems, was 102,000 IU/ml, reported in a paper I published in 1978 (Vilcek et al., pages 101-118, in *Human Interferon: Production and Clinical Use,* Stinebring and Chapple, eds., Plenum Press, 1978).... At the time, there appeared to be an upper limit to the amount of IFN that could be produced and secreted by animal cells.

Vilcek Decl. (Mar. 27, 1997), Bassett Aff. Ex. 7, at 133-34.

On June 10, 1997, the Examiner allowed some claims of the '779 Patent, stating that the Vilcek Declaration was "sufficient to overcome the rejection" for obviousness. Bassett Aff. Ex. 7, at 171-72. On September 9, 1997, Berlex first advised the Patent Office of the instant litigation involving the '567 Patent, which commenced on May 3, 1996. Id. at 189-94. The '779 Patent issued on August 18, 1998. '779 Patent, Bassett Aff. Ex. 3.

F. ***Biogen's Avonex Process and Product***

Biogen produces Avonex from interferon that has been secreted from transformed CHO cells. As indicated earlier, in contrast to Berlex, Biogen utilizes a process of unlinked co-transformation. Blx's LR 56.1 Statement of Undisputed Facts in Connection with its Mot. for Summ. J. that Bg Literally Infringes Certain Claims of U.S. Patent Nos. 5,367,567 and 5,795,779 ("Blx Literal Infringement Facts") para. 9. More specifically, Biogen introduces interferon into CHO cells on one DNA construct and the DHFR selectable marker on a separate construct.

It has been stipulated that the nine bioassays performed for Biogen by Dr. Wendy Jones are reliable. Stipulation (Jan. 14, 2000). Those nine tests resulted in the measurement of 1,200,000 IU/ml two times, 1,500,000 IU/ml six times, and 1,600,000 IU/ml one time. Id. In the process of achieving an interferon concentration of 1,200,000-1,600,000 IU/ml, Biogen's product goes through the 150,000-600,000 IU/ml range. Mar. 10, 2000 Tr. at 41.

IV. BERLEX'S MOTION FOR SUMMARY JUDGMENT CONCERNING LITERAL INFRINGEMENT OF THE '567 PATENT

Berlex has moved for summary judgment on its assertion that some, but not all, of the claims in the '567 Patent are literally infringed by Biogen. As discussed previously, the '567 Patent includes some claims that do not expressly refer to the use of a single DNA construct containing both an interferon gene and DHFR as the selectable marker. Thus, Berlex contends that Biogen's use of multiple constructs to introduce interferon and DHFR into cells literally infringes those claims.

Biogen asserts, however, that each of the claims in the '567 Patent include terms which require clarification by reference to the specification and prosecution history. Biogen argues that when the specification and prosecution history are consulted, a person of ordinary skill in the relevant art would understand that each of the claims in the '567 Patent is limited to the use of a single DNA construct and, therefore, Biogen'smethod of producing Avonex does not literally infringe the '567 Patent.

[3] "An infringement analysis entails two steps. The first step is determining the meaning and scope of the patent claims asserted to be infringed. The second step is comparing the properly construed claims to the device accused of infringing." Kraft Foods, Inc. v. International Trading Co., 203 F.3d 1362, 1366 (Fed.Cir.2000) (citation and internal quotations omitted). Claim construction is a question of law to be decided by the court. Markman v. Westview Instruments, Inc., 517 U.S. 370, 372, 116 S.Ct. 1384, 134 L.Ed.2d 577 (1996) (" *Markman II* "). The parties agree that there are no facts material to the question of whether the '567 Patent is literally infringed that are genuinely in dispute. Thus, after the court construes the claims at issue, the question of literal infringement may be resolved as a matter of summary judgment. Athletic Alternatives, Inc. v. Prince Mfg. Inc., 73 F.3d 1573, 1578 (Fed.Cir.1996).

For the reasons described below, the court concludes that Biogen's proposed claim construction is correct and that each of the claims of the '567 Patent requires the use of a single DNA construct that includes an interferon gene and a DHFR marker gene. Therefore, Biogen's method of introducing interferon genes and DHFR marker genes into cells on separate DNA constructs does not literally infringe the '567 Patent. Accordingly, Berlex's motion for summary judgment on this issue is being denied. Instead, judgment must be entered for Biogen on the claim of literal infringement of the '567 Patent.

In construing the claims of the '567 Patent, the court has considered the purposes of the patent laws and patents, as well as the principles of claim construction enunciated primarily by the Court of Appeals for the Federal Circuit. These include the following.

The Patent Clause [of the Constitution] reflects a balance between the need to encourage innovation [by granting monopoly power over the production, use, and sale of the patented product] and the avoidance of monopolies which stifle competition without any concomitant advance in the "Progress of Science and useful Arts." ... the federal patent laws have embodied a careful balance between the need to promote innovation and the recognition that imitation and refinement are both necessary to invention itself and the very lifeblood of a competitive economy.

Bonito Boats, Inc. v. Thunder Craft Boats, Inc., 489 U.S. 141, 146, 109 S.Ct. 971, 103 L.Ed.2d 118 (1989).

[4] [5] "A patent is a government grant of rights to the patentee." Markman v. Westview Instruments, Inc., 52 F.3d 967, 978 (Fed.Cir.1995) (en banc) (" *Markman I* "). Among other things, it gives the patentee rights, for a limited period of time, to exclude others from using the invention claimed. *Id*. In order not to stifle innovation and competition unduly, however, "[t]he public generally, and in particular, the patentee's competitors, are entitled to clear and specific notice of what the inventor claims as his invention." Exxon Chem. Patents, Inc. v. Lubrizol Corp. (" Luorizol "), 64 F.3d 1553, 1563 (Fed.Cir.1995) (Plager, J., concurring). *See also* Markman I, 52 F.3d at 978. Such clear notice informs a competitor, who may be contemplating an expensive investment, of what is permissible. It also provides that competitor assurance that "if infringement litigation occurs, [ ] a judge, trained in the law, will similarly analyze the text of the patent and its associated public record and apply the established rules of construction, and in that way arrive

at the true and consistent scope of the patent owner's rights to be given legal effect." *Id*. at 979.

[6] [7] A patent's claims define the scope of the protection that the patent provides. Renishaw PLC v. Marposs Societa' per Azioni, 158 F.3d 1243, 1248 (Fed.Cir.1998). "[T]he claim construction inquiry, therefore, begins and ends in all cases with the actual words of the claim." *Id*. Evidently because the primary audience is potential competitors seeking notice of what is protected and what is permissible, the words used in the claims must be construed from the perspective of the person ordinarily skilled in the field of invention. *The* Toro Co. v. White Consol. Indus., Inc., 199 F.3d 1295, 1299 (Fed.Cir.1999).

[8] [9] Claims must be read in the context of the specification and prosecution history, as a person skilled in the art would read them. Markman I, 52 F.3d at 979-80; Vitronics Corp. v. Conceptronic, Inc., 90 F.3d 1576, 1582 (Fed.Cir.1996); Bell Communications Research, Inc. v. Vitalink Communications Corp., 55 F.3d 615, 619-20 (Fed.Cir.1995). "[T]he specification is always highly relevant to the claim construction analysis. Usually, it is dispositive; it is the single best guide to the meaning of a disputed term." Vitronics, 90 F.3d at 1582. *See also* Bell Communications, 55 F.3d at 621. If a term used in a claim has "a clear and well-defined meaning" for those skilled in the art, "limitations from the specification are not to be read into the claims." Comark Communications, Inc. v. Harris Corp., 156 F.3d 1182, 1186-87 (Fed.Cir.1998). "[T]here must be a textual reference in the actual language of the claim with which to associate a proffered claim construction." Johnson Worldwide Assoc., Inc. v. Zebco Corp., 175 F.3d 985, 990 (Fed.Cir.1999).

However, as the Court of Appeals for the Federal Circuit has held in a series of recent decisions, terms as seemingly straightforward as "protecting," "frame," "included," and "when" may require clarification by reference to the specification and prosecution history. *See* Kraft Foods, 203 F.3d at 1368 ("protecting"); Wang Labs., Inc. v. America Online, Inc., 197 F.3d 1377, 1380 (Fed.Cir.1999) ("frame"); Toro, 199 F.3d at 1299 ("included"); Renishaw, 158 F.3d at 1250 ("when"). The foregoing cases indicate that the context of the words in claims is critical to understanding their meaning. "[T]he interpretation to be given a term can only be determined and confirmed with a full understanding of what the inventors actually invented and intended to envelop with the claim." Renishaw, 158 F.3d at 1250. The specification and prosecution history illuminate what was invented and intended to be covered by a claim. *See* Comark, 156 F.3d at 1187 (specification should be consulted "to ascertain the meaning of a claim term as it is used by the inventor in the context of the entirety of his invention").

[10] "There is presumed to be a difference in meaning and scope when different words or phrases are used in separate claims. To the extent that the absence of such difference in meaning and scope would make a claim superfluous, the doctrine of claim differentiation states the presumption that the difference between claims is significant." *Id*. (quoting Tandon Corp. v. United States Int'l Trade Comm'n, 831 F.2d 1017, 1023 (Fed.Cir.1987)). That presumption, however, is rebuttable. Comark, 156 F.3d at 1187. "[T]he doctrine of claim differentiation does not serve to broaden claims beyond their meaning in light of the specification and does not override clear statements of scope in the specification and the prosecution history." Toro, 199 F.3d at 1302.

[11] The court has construed the claims of the '567 Patent by applying the foregoing principles. The court has considered the language of the claims at issue in light of the other intrinsic evidence-the specification and prosecution history.FN11 Read in context, those claims contain terms that require clarification. Thus, the court has employed the specification and prosecution history, as well as the words of the claims themselves, to determine what the claims would communicate to a person skilled in the art who was seeking to determine what was protected by the '567 Patent and what was fair game for innovation.

FN11. The court has not based its decision concerning the literal infringement of the '567 Patent on any extrinsic evidence, including the May 28, 1999 Declaration of Dr. Saul J. Silverstein that was submitted by Biogen.

The '567 Patent includes four sets of claims that do not expressly reference a single DNA construct that includes an interferon gene and a DHFR gene. Berlex asserts that Biogen literally infringes each of these claims.

Two of the independent claims at issue are characterized by Berlex as method claims. These are:

42. A method for the production of human interferon in a Chinese hamster ovary cell, comprising growing a Chinese hamster ovary cell having incorporated therein a DNA construct comprising human (alpha)- or (beta) interferon gene, which construct is effective for expression of said human interferon gene, under conditions whereby the interferon gene in said construct is expressed.FN12

FN12. Dependent Claims 43, 44, 45, 52, 56, 58, and 64 rely on Claim 42. '567 Patent, Bassett Aff. Ex. 2, at 29:26-37, 59-60, 30:1-2, 6-7, 33-34. Berlex asserts that Biogen literally infringes these claims. With regard to all of the dependent claims at issue, if the related independent claim is not literally infringed, the dependent claim is not literally infringed either.

and
70. A method of producing human interferon comprising growing a progeny cells of a Chinese hamster ovary cell which has been transformed with an expressible interferon gene and an expressible gene for dihydrofolate reductase, under conditions effective for expression of said human interferon gene.FN13

FN13. Berlex asserts that Biogen literally infringes Claims 72 and 78 which rely on Claim 70. *See* '567 Patent, Bassett Aff. Ex. 2, at 30:58-60, 31:6-7.

'567 Patent, Bassett Aff. Ex. 2, at 29:18-25, 20:50-55.

Two of the other independent claims are characterized by Berlex as cell claims. These are:

66. A Chinese hamster ovary cell having incorporated therein an expressible gene encoding human (alpha)- or (beta)interferon, or a progeny thereof. FN14

FN14. Berlex also asserts dependent Claim 67 against Biogen. *See* '567 Patent, Bassett Aff. Ex. 2, at 30:40-42.

and
68. A Chinese hamster ovary cell having incorporated into its chromosome an expressible gene encoding human interferon, or a progeny thereof.FN15

FN15. Claim 69 depends on Claim 68 and is asserted to be literally infringed by Biogen. *See* '567 Patent, Bassett Aff. Ex. 2, at 30:46-48.

Id. at 30:37-39, 30:43-45.

Both viewed in isolation, and particularly in the context of the other intrinsic evidence, each of these claims includes terms that require scrutiny of the specification and prosecution history to be clarified and understood for the purpose of determining what the '567 Patent protects. Claim 42 requires a CHO cell "having incorporated therein a DNA construct" that is "effective for expression" "under conditions whereby the interferon gene in said construct is expressed." Id. at 29:20-25. These terms require interpretation and can only be properly understood in context. The terms of the claim are unclear concerning how the function described is to be performed. For example, read in the context of the construct claims, a person skilled in the art would wonder whether Claim 42 requires incorporation of the interferon gene by a particular method. Such a person would presumably be familiar with the claim differentiation doctrine, which would suggest that Claim 42 does not require use of a single DNA construct, but also know that any such presumption may be rebutted by the specification and prosecution history. Toro, 199 F.3d at 1302.

Similarly, Claim 70 requires a CHO cell (1) "which has been transformed with" (2) "an expressible interferon gene and an expressible gene for" DHFR (3) "under conditions effective for expression of said interferon gene. " '567 Patent, Bassett Aff. Ex. 2, at 30:50-55. Once again, reading this claim in the context of the other claims, a person of ordinary skill in the art would question whether the CHO cells must be transformed in a particular manner and, especially, whether a single DNA construct including interferon and DHFR is required to transform the cells in a fashion that is effective for the production of interferon.

Claims 66 and 68 essentially raise the same questions as Claim 42. A person skilled in the art would be uncertain of the meaning of the terms "having incorporated therein" and "expressible gene" as they are used in this patent.

If a person skilled in the art looked initially at major parts of the specification and prosecution history, it would be evident that, as used in the '567 Patent, the disputed terms do not have a "clear and well-defined meaning." Comark, 156 F.3d at 1187. Rather, they must be clarified by reference to the specification and prosecution history. *See, e.g.,* Kraft Foods, 203 F.3d at 1368.

For example, the Summary of Invention begins by describing "[t]he present invention" as " *a DNA construct* for the expression of the human interferon gene" in CHO cells "comprising an operable linkage of" a selectable marker and a human interferon gene. '567 Patent, Bassett Aff. Ex. 2, at 2:33-46 (emphasis added). The Summary goes on to explain that the "present invention also provides a method for producing human interferon in CHO cells" by "introducing into" them " *the above-described DNA construct*." Id. at 2:52-56 (emphasis added). The Summary also states that, "[i]n yet another aspect, the invention provides human interferon *produced by the above method*.... " Id. at 2:64-65 (emphasis added). This language suggests that a single DNA construct, including both an interferon gene and DHFR, is required by all of the claims in the '567 Patent. This impression would be strengthened by a review of the four relevant diagrams in the specification, each of which depicts a single DNA construct including both a human interferon gene and a selectable marker. Id. at Figs. 1-4.

Similarly, the prosecution history on public record makes it clear that there is at least a serious question

concerning whether every claim added in the '567 Patent requires the use of a single DNA construct. For example, the last item in the public file is the Notice of Allowability of certain amendments to the claims of the '843 Patent, which emerged as the '567 Patent. Bassett Aff. Ex. 6, at 335-36. After listing all of the allowed claims, the Patent Examiner wrote:

Applicants['] claims are directed to *a DNA construct comprising a vector, an interferon gene, and a dhfr marker gene*. The construct is expressed in CHO cells. The instant claims are similar to the claims in parent Patent 4,966,843 ('843), however the instant claims recite the marker gene to be dhfr, whereas the '843 claims do not. Since a terminal disclaimer has been filed over the '843 claims, the instant claims are held allowable.

Id. at 336 (emphasis added).

Reading this entry would influence a person skilled in the art to conclude at least that there are terms in Claims 42, 66, 68, 70 that require clarification. Neither such a person, nor the court, could properly end the inquiry by considering only the Summary, the diagrams, and the Reasons for Allowance. Amhil Enters. Ltd. v. Wawa, Inc., 81 F.3d 1554, 1559 (Fed.Cir.1996) ("The entire specification, including all of the claims, the prosecution history, and the prior art may all affect the interpretation ultimately placed on claim language."). However, the necessary close examination of all the intrinsic evidence demonstrates that there are terms in each of the disputed claims that require clarification and that all of those claims, properly construed, require the use of a single DNA construct.

The specification as a whole must be considered in determining what the '567 Patent protects. *See* Hyatt v. Boone, 146 F.3d 1348, 1353 (Fed.Cir.1998). The title of the '567 Patent is "Expression of Interferon Genes in Chinese Hamster Ovary Cells." While this title tends to support Berlex's claim that a single DNA construct is not essential to the invention protected, Berlex does not rely on this fact because it recognizes that the Court of Appeals for the Federal Circuit has noted "[t]he near irrelevancy of the patent title to claim construction." Pitney Bowes, Inc. v. Hewlett-Packard Co., 182 F.3d 1298, 1312 (Fed.Cir.1999).

The Court of Appeals for the Federal Circuit has recently explained that courts may consider the abstract because the abstract is a "potentially helpful source of intrinsic evidence as to the meaning of claims." Hill-Rom Co., Inc. v. Kinetic Concepts, Inc., 209 F.3d 1337, 1341 n. *, (Fed.Cir.2000). In this case, the abstract is relevant. It states, in pertinent part, that:

DNA constructs are prepared which operably link human interferon genes, selective, eukaryotic marker genes, and promoter and expression control sequences for the expression of human interferon in Chinese hamster ovary (CHO) cells or progeny thereof.

'567 Patent at BG0035689. Thus, the abstract supports Biogen's view that the disputed claim should be interpreted as being limited to a single DNA construct.

Each of the four figures in the specification depicting constructs shows a single DNA construct with both a human interferon gene and a selectable marker gene. Id. Figs. 1-4, at BG0035690-91. No drawing shows the interferon and marker genes on separate constructs. Thus, the relevant drawings support Biogen's proposed construction of the disputed claims.

The Background of Invention states that, "[t]his application relates to human interferons and their

production in Chinese hamster ovary cells ..." Id. at 1:14-15. It is Berlex's position that the protected invention is the production of human interferon in CHO cells, rather than the means used to transform those cells to achieve that result. This statement is consistent with that contention.

However, in seeking to distinguish the Axel International Patent, the Background of Invention characterizes the "transforming vectors" and "methods for transformation" as "essential components" for enabling interferon expression. Id. at 2:23-26. This language supports Biogen's position that the use of the single DNA construct described and depicted in the specification is an "essential component" of all aspects of the invention disclosed in the '567 Patent.

As described earlier, the Summary of Invention describes the "present invention" as: "a DNA construct" with both a human interferon gene and a selectable marker; a method for producing human interferon by "introducing into" CHO cells "the above-described DNA construct;" and providing human interferon "produced by the above method." Id. at 2:30-33. Thus, the sole embodiment of the claimed invention actually referenced in the Summary requires a single DNA construct.

The Summary concludes by stating that "[i]n preferred embodiments, DNA fragments ... [are] introduced into CHO cells by DNA transfection, or by penetration of viral vectors carrying the DNA fragment, or by transfection of cloned plasmids ..." Id. at 2:67-3:4. Consistent with this, there is later language in the specification that defines the term "DNA construct" as "any suitable cloning vector." Id. at 5:21-22. The specification also states that, "[i]n accordance with the present invention, any approach may be used to introduce the cloned DNA into CHO cells." Id. at 15:44-46. Three possible approaches are then mentioned: DNA transfection, use of an animal virus, and cloned plasmids. Id. at 15:48-16:41. Although Berlex's expert opines that viral transfection "would not be expected to involve the use of a selectable marker gene," it appears that each of the three methods mentioned would be compatible with the use of a single DNA construct that includes a human interferon gene and a selectable marker. Mar. 7, 2000 Tr. at 77-79; Hiscott Reb. Rpt., Gillum Decl., Ex. 2, at 51.

In any event, as Berlex has acknowledged, this general language about the possible use of any approach to introduce cloned DNA into CHO cells is inconsistent with a more detailed discussion in the specification which states that the patented method for producing human interferon involves a DNA construct which includes a human interferon gene operably linked to a selectable marker gene. *See* Mar. 7, 2000 Tr. at 74-76. The language that Berlex recognizes is inconsistent with its position states that:

The method of effecting expression of heterologous genes in CHO host cells or progeny thereof generally involves *preparing DNA constructs as defined above operably linked to* a nucleotide sequence for replicating in a prokaryotic cell, preferably E. coli; *a marker gene operably linked to a CHO cell selectable marker* for the selection of transformants or progeny thereof, and operably linked to a promoter and start and stop codons; *and an interferon gene from a human source, operably linked to an endogenous or heterologous promoter* and translation sequences (start and stop codons) for expression of the interferon gene in CHO cells or progeny thereof. *This DNA construct is then introduced in CHO cells or progeny thereof, preferably in a culture, by any technique, including any of the three techniques described below,* the transformed cells are selected and then grown under selective conditions whereby the interferon gene is expressed; and the interferon so produced is isolated and purified.

'567 Patent at 5:64-6:16 (emphasis added). This language again indicates that a single DNA construct is contemplated by all of the claims in the '567 Patent.

It is undisputed that the inventors of the '567 Patent and its predecessors never transformed CHO cells using any method other than the introduction of a single DNA construct with a human interferon gene and a selectable marker. *See* Mar. 8, 2000 Tr. at 19. Nevertheless, the specification concludes with the statement that:

The foregoing description of the preferred embodiments of the instant invention have been presented for purposes of illustration and description. It is not intended to be exhaustive or to limit the invention to the precise forms disclosed.

'567 Patent at 27:7-12. Thus, Berlex argues that any limitation suggested by the specification should not be read into the disputed claims. *See* Johnson Worldwide, 175 F.3d at 989-90; Laitram Corp. v. Cambridge Wire Cloth Co., 863 F.2d 855, 865 (Fed.Cir.1988).

The instant case, however, is analogous to the trilogy of cases recently decided by the Federal Circuit, *Krafts Foods, Toro,* and *Wang*. In each of those cases, broad language in the claims was construed as being limited in part because the device shown in the specification and characterized as the "preferred embodiment" was actually the only embodiment of the invention that was disclosed. *See* Kraft Foods, 203 F.3d at 1368; Toro, 199 F.3d at 1301; Wang, 197 F.3d at 1383. As the Court said in *Wang,* "[w]hether an invention is fairly claimed more broadly than the 'preferred embodiment' in the specification is a question specific to the content of the specification, the context in which the embodiment is described, the prosecution history, and if appropriate the prior art, for claims should be construed, when feasible, to sustain their validity." Wang, 197 F.3d at 1383.

Wang is particularly instructive for the instant case. In *Wang,* the Federal Circuit affirmed the district court's granting of summary judgment of non-infringement. The patent at issue in *Wang* covered an apparatus for providing users with text and graphics from computer controlled databases via a telephone network. *Id*. at 1379-80. Wang Laboratories, the patentee, claimed that the patent was infringed by Netscape's "bookmark" feature and by America On-Line's ("AOL") "favorite places" feature. *Id*. at 1379.

The key claim construction issue in *Wang* was the interpretation of the word "frame." AOL and Netscape contended that the word "frame" should be limited to the "character-based systems" described in the patent's specification. *Id*. at 1381. Wang, on the other hand, contended that term should be construed, in accordance with the term's "general usage," to include both character-based systems and bit-mapped systems of the sort used by Netscape and AOL. *Id*.

In deciding the issue, the Federal Circuit acknowledged that the term "frame," in general usage, could be applied to both bit-mapped and character-based systems. *Id*. It nevertheless held that, for the purpose of construing the claim, the general usage of the term was less probative than how one skilled in the art would understand the term in light of the patent's specification. Specifically, the Court noted that: the only embodiment described in the invention was the character-based protocol, *id*. at 1382; the specification consistently illustrated the word "frame" with only a character-based protocol, *id*. at 1383; references to other protocols did not indicate that they were to be included within the scope of the invention, *id.;* and during the prosecution of the parent patent application, Wang had distinguished its invention over a prior art reference on the grounds that the prior art used a bit-mapped protocol, rather than a character-based protocol, *id*. at 1384.

Therefore, the Court of Appeals for the Federal Circuit held that the "only system that [was] described and enabled in the [patent's] specification and drawings uses a character-based protocol." *Id*. at 1382. The Court then noted that, "it is not disputed that Wang had not been able to implement a bit-mapped protocol in the claimed system." *Id*. Wang contended that this fact was relevant only to the issue of validity and "not a factor in claim construction." *Id*. at 1383. The court, however, held that "claims are not properly construed to have a meaning or scope that would lead to their invalidity." *Id*.

The instant case is analogous to *Wang*. As described earlier, the Summary of Invention describes all aspects of the invention as including a single DNA construct that includes a human interferon gene and a selectable marker. '567 Patent, at 2:33-46. All four figures displaying constructs depict that single DNA construct. Id. Figs. 1-4. The inventors of the '567 Patent never used anything but a single DNA construct to transform a CHO cell. In addition, as discussed below, the prosecution history indicates that the patent was granted to protect only the use of a single DNA construct. Thus, the court concludes that a single DNA construct was essential to all of the claims in the '567 Patent. Moreover, although the court does not rely on this fact, if the claims at issue were construed as Berlex suggests, they, like the claims in *Wang,* would probably be invalid because the written description is inadequate to satisfy the written specification requirement of 35 U.S.C. s. 112. Digital Biometrics, Inc. v. Identix, Inc., 149 F.3d 1335, 1346 (Fed.Cir.1998); Laitram Corp. v. Morehouse Indus., Inc., 143 F.3d 1456, 1463 (Fed.Cir.1998).

Analysis of the prosecution history also supports the view that all of the claims in the '567 Patent require the use of a single DNA construct. As described in detail in s. III, *supra,* the original 1982 application was based on the hypothesis that the use of a single DNA construct was superior to Axel's method of promoting transformation and production of interferon, which was erroneously characterized as requiring the use of multiple constructs. Ringold Dep., Battin Decl. Ex. 15, at 65. Nevertheless, the Examiner rejected the claims as obvious in terms of the prior art. Bassett Aff. Ex. 4, at 45-48.

The inventors then amended their claims to require expressly a linkage of an interferon gene, a selectable marker, and a replication sequence. Id. at 75-77. They characterized their invention as the construction of *a* plasmid which, when introduced into CHO cells, would produce human interferon in large quantities without also producing hamster interferon. Id. at 81-82. They emphasized that "[t]hese unexpected and advantageous results were accomplished by linking the interferon gene with the gene containing the selectable marker on a *single* DNA construct." Id. at 82 (emphasis in original). The inventors asserted that the use of a single plasmid distinguished their invention from Axel's prior art. Id. at 83. Although this contention was erroneous, a person skilled in the art would understand that the inventors were then limiting their claims to the use of a single DNA construct.

The 1985 CIP application continued to rely on a single DNA construct. As also described in detail in s. III, *supra,* it added the diagrams and the Summary depicting and describing the invention as including, in all of its aspects, a single DNA construct.

The 1985 CIP application resulted in the issuance of the '843 Patent. It is undisputed that the '843 Patent requires the use of a single DNA construct and is not literally infringed by Biogen.

The 1990 Divisional application filed by Cetus continued to characterize the invention as dependent upon a single DNA construct. Bassett Aff. Ex. 6, at 114. A person skilled in the art reading the prosecution history after Berlex acquired the rights to the invention in 1991 would understand that Berlex attempted to broaden the claims to protect more than a single DNA construct, but that its effort failed.

More specifically, in 1992 Berlex filed a preliminary amendment. Id. at 156. In its submission Berlex included proposed claims that evolved into the claims in the '567 patent that Berlex now contends are literally infringed.

Claim 71 later emerged as Claim 42 of the '576 patent. Claim 71 stated:

A method for the production of human interferon or a mutein thereof in a Chinese hamster ovary cell or progeny thereof comprising:

growing a Chinese hamster ovary cell or progeny thereof *transformed with* a DNA construct for expression in a Chinese hamster ovary cell or progeny thereof comprising a human interferon gene or a gene coding for a mutein of human interferon which retains the biological activity of said interferon, *said construct being effective for transcription and translation* of said gene *when introduced into* a Chinese hamster ovary cell or progeny thereof,

under conditions whereby said gene in said construct is expressed.

Id. at 160 (emphasis added).

Claim 104 became Claim 66 in '587 Patent. Claim 104 states:

A Chinese hamster ovary cell or a progeny thereof *having incorporated into* its chromosome a DNA construct of claim 47.

Id. at 163 (emphasis added).

Claim 108 became Claim 68 in the '567 Patent.

A Chinese hamster ovary cell or a progeny thereof *transformed with* a DNA construct of claim 47.

Id. at 164 (emphasis added).

Claim 70 did not have a progenitor in the initial preliminary amendment. Id. at 208.

The Examiner rejected all of the proposed new claims, including 71, 104, and 108 because of obvious-type double patenting Id. at 173, 175. While she recognized that the claims were not identical, she stated: "The DNA construct, either described by its physical elements or by its function, is the same in the prior patent and the instant application." Id. at 175. The functional language to which the Examiner referred included the underlined terms in Claims 71, 104, and 108: "transformed with," "effective for transcription and translation," "introduced into" and "having incorporated into."

Berlex addressed the rejection by filing a terminal disclaimer. Id. at 185. This satisfied the Examiner with regard to Claims 29-46, but did not overcome her objections to the predecessors of the claims now in dispute, original Claims 71, 104, and 108. They were rejected again. Id. at 193-95.

Berlex subsequently agreed to narrow all of what it characterized as its "construct claims" to require DHFR

rather than any other marker gene. Id. at 200. The Examiner initially wrote in her Interview Summary Record, "claims will be narrowed." Id. at 200. At Berlex's request, she added several words, so her description of the agreement that she had reached with Berlex finally stated, "Construct claims will be narrowed to include DHFR marker." Id.

At the time this comment was written, the Examiner had found all of the proposed new claims to be the functional equivalent of the invention in the '843 Patent, which in all of its aspects required a single DNA construct. Read in context, this comment indicates that Berlex was seeking to make a distinction between what it characterizes as "construct claims" as opposed to "cell" or "method" claims. The record indicates, however, that the Examiner viewed all of the proposed claims as including the functional equivalent of the single DNA construct and had agreed to allow the earlier versions of the '567 Patent's Claims 42, 66 and 68, among others, because all of the claims were being limited by the restriction to DHFR as the marker gene.

Berlex subsequently filed an Amendment which the Examiner viewed as consistent with the agreement previously reached. The Amendment included new versions of the claims that were eventually included in the '567 Patent as Claims 42, 66, and 68. Id. at 201-07. It also included a proposed Claim 110, that emerged in the '567 patent as Claim 70. That Claim stated:

A method of producing human interferon comprising growing a progeny of a Chinese hamster ovary cell *which has been transformed* with an expressible interferon gene and an expressible gene for dihydrofolate reductase, under conditions effective for expression of said human interferon gene.

Id. at 208 (emphasis added).

In its remarks accompanying the Amendment, Berlex stated that its "claims continue to reflect the pioneering invention of the first expression of interferon (IFN) genes in Chinese hamster ovary cells." Id. at 213. Berlex also stated that this invention did "not depend in any particular nucleic acid construct configuration." Id. at 223. Berlex did not assert that its invention did not depend on a single DNA construct. It did note, however, that contrary to the representations of the original inventors, Axel had disclosed linked as well as unlinked genes, but argued that it was "not relevant" whether Axel employed only unlinked co-transformation. Id.

The prosecution history also demonstrates that the Examiner did not accept Berlex's view and did not grant a patent as broad as Berlex sought. In her Notice of Allowability, she identified all of the claims being allowed. Id. at 335-36. She then stated the "Reasons for Allowance" quoted earlier:

Applicants[']claims are directed to a DNA construct comprising a vector, an interferon gene, and a dhfr marker gene. The construct is expressed in CHO cells. The instant claims are similar to the claims in parent Patent 4,966,843 ('843), however the instant claims recite the marker gene to be dhfr, whereas the '843 claims do not. Since a terminal disclaimer has been filed over the '843 claims, the instant claims are held allowable.

Id. at 336. This statement communicates to the court, as it would to a person skilled in the art, that *all* claims involved a single DNA construct which included an interferon gene and a DHFR gene.

The prosecution history also implicitly explains why the claims now at issue were so construed by the Examiner. Each of Claims 42, 66, 68, and 70 of the '567 Patent include terms that the Examiner previously

found to be the unpatentable functional equivalent of the claims expressly reciting the single DNA construct, such as "having incorporated therein" or "incorporated into" (Claims 42, 66, 68), or "transformed with" (Claim 70). While only Claim 42 expressly stated that it was "a DNA construct" that was being incorporated, the court infers and finds that the Examiner believed that the language in Claim 70, "transformed with an expressible interferon gene and an expressible gene for [DHFR], under conditions effective for expression" of human interferon, was synonymous with the use of a single DNA construct, and reached the same conclusion concerning the language of Claims 66 and 68 as well. Thus, the presence of a DHFR marker as part of a single DNA construct was essential to the invention covered by all of the claims allowed as part of the '567 Patent.

The Examiner's Reasons for Allowance are the last entry in the public record. Although Berlex later sent the PTO a "Comments on Statement of Reasons for Allowance" seeking to assert broader claims than the Examiner allowed, this is not part of the prosecution history available to the person skilled in the art seeking to determine what was protected and what was permissible after the issuance of the '567 Patent. Mar. 8, 2000 Tr. at 18. Thus, this court may not consider that submission either.

Accordingly, careful consideration of the intrinsic evidence would educate a person skilled in the art to understand that the claims in dispute included terms that required clarification and, when viewed in the context of the specification and prosecution history, all of the claims require the use of a single DNA construct which includes an interferon gene and a DHFR gene.

The court recognizes that this construction of the disputed claims causes some of the claims of the '567 Patent to be superfluous. Biogen's proposed construction of Claim 66 would render it exactly commensurate to Claim 36 in scope. This raises the presumption that Claims 36 and 66 have different scopes and that Claim 66 is not limited to the use of a single DNA construct. However, as described earlier, the doctrine of claim differentiation only establishes a presumption. Toro, 199 F.3d at 1302; Kraft Foods, 203 F.3d at 1368. "Claim differentiation cannot broaden claims beyond their correct scope." Kraft Foods, 203 F.3d at 1368. *See also* ATD Corp. v. Lydall, Inc., 159 F.3d 534, 541 (Fed.Cir.1998). In this case, the import of the specification and prosecution history are clear. Thus, the presumption that the distinctive words used in Claims 42, 66, 68, and 70 give each of those claims unique scope has been rebutted. *See* Toro, 199 F.3d at 1302.

Therefore, Berlex's motion for summary judgment on its claim of literal infringement of the '567 Patent is being denied. Summary judgment shall be entered for Biogen on this issue.

V. BIOGEN'S MOTION FOR SUMMARY JUDGMENT CONCERNING INFRINGEMENT OF THE '567 PATENT **UNDER THE DOCTRINE OF EQUIVALENTS**

The '567 Patent includes a number of claims which refer expressly to "a DNA construct" and by their terms require the use of a single DNA construct that includes an interferon gene and a DHFR gene. Berlex does not contend that Biogen's use of separate DNA constructs with only an interferon gene on one construct and a DHFR gene on another construct literally infringes what it calls its "single construct claims." Berlex does allege, however, that Biogen infringes those claims under the doctrine of equivalents.

Biogen has moved for summary judgment on this issue. For the reasons described below, the undisputed material facts demonstrate that prosecution estoppel bars Berlex's claim of infringement of the '567 Patent based on the doctrine of equivalents. Therefore, Biogen's motion for summary judgment is being allowed.

The independent claims at issue in this motion are Claims 1, 40, 87 and 90.FN16 Each of these claims expressly recites a DHFR gene and an IFN gene on a single DNA construct.

FN16. Biogen also seeks summary judgment on the dependent claims of Claims 1, 40, 87, and 90. Because a finding of non-infringement of the independent claims mandates a finding that the dependent claims are not infringed, the court is not separately considering limitations added by the dependent claims except for Claims 46, 73-77, and 81-83, dependent claims which include an "operable linkage" limitation.

Claim 1 is illustrative. It states:

A DNA construct for expression in a Chinese hamster ovary cell comprising a human interferon gene and a dihydrofolate reductase gene, said construct being effective for transcription and translation of said interferon gene in a Chinese hamster ovary cell into which it has been introduced or in progeny cells thereof.

'567 Patent, Bassett Aff. Ex. 2, at 27:22-27.

Claim 40 is similarly directed to a DNA construct comprising interferon and DHFR.FN17

FN17. Claim 40 recites: "A DNA construct useful for expression of an interferon in a Chinese hamster ovary cell comprising a gene coding for a human interferon and a gene coding for dihydrofolate reductase capable of functioning as a selectable marker, said construct being effective for transcription and translation of said genes in a Chinese hamster ovary cell into which it has been introduced or in progeny thereof, which is incorporated into said Chinese hamster ovary cell chromosome when it is introduced therein, and which is effective for increasing the copy number of said interferon gene when incorporated into a Chinese hamster ovary cell." '567 Patent, Bassett Aff. Ex. 2, at 29:4-15.

Claim 90 is essentially the same as Claim 1, except the words "nucleic acid construct" are substituted for "DNA construct" and the words "nucleic acid sequence" encoding for interferon and DHFR are substituted for "genes." FN18

FN18. Claim 90 is directed to: "A nucleic acid construct for expression in a Chinese hamster ovary cell, comprising a nucleic acid sequence coding for human interferon and a nucleic acid sequence coding for dihydrofolate reductase, said construct being effective for transcription and translation of said nucleic acid sequences in a Chinese hamster ovary cell into which it has been introduced or in progeny cells thereof. " '567 Patent, Bassett Aff. Ex. 2, at 32:18-25.

Claim 87 provides protection to "a method of producing human interferon" comprising growing the progeny of a CHO cell that has been transformed with "a DNA construct which comprises *an operable linkage* of the genes for said human interferon and for dihydrofolate reductase each operably linked to promoter ...." FN19 (emphasis added).

FN19. Claim 87 describes: "A method of producing human interferon comprising growing progeny cells of

a Chinese hamster ovary cell which has been transformed with a DNA construct which comprises an operable linkage of the genes for said human interferon and for dihydrofolate reductase each operably linked to a promoter, and wherein said Chinese hamster ovary cell was dihydrofolate reductase deficient prior to said transformation and said interferon is IFN-(beta), said growing being conducted under conditions effective for expression of human IFN-(beta)." '567 Patent, Bassett Aff. Ex. 2, at 32:1-11.

[12] [13] There are two defenses to a claim of infringement under the doctrine of equivalents. Warner-Jenkinson Co. v. Hilton Davis Chem. Co., 520 U.S. 17, 117 S.Ct. 1040, 137 L.Ed.2d 146 (1997) (" *Hilton Davis* "). First, prosecution history estoppel may bar such a claim. Second, under the "all elements" rule, there is no infringement under the doctrine of equivalents unless every limitation in a claim is infringed either literally or equivalently by some insubstantial variation. *Id*. at 29, 40, 117 S.Ct. 1040. If prosecution history estoppel is established, it is not necessary to decide whether the all elements test is met. American Permahedge, Inc. v. Barcana, Inc., 105 F.3d 1441, 1445-46 (Fed.Cir.1997); Morehouse Indus., 143 F.3d at 1464; Texas Instruments, Inc. v. United States Int'l Trade Comm'n, 988 F.2d 1165, 1174 (Fed.Cir.1993).

The facts concerning the relevant prosecution history are not in dispute, although the parties differ on the legal implications of them. Therefore, Biogen's assertion that the prosecution history bars Berlex's attempt to establish infringement under the doctrine of equivalents is amenable to being resolved as a matter of summary judgment. Hilton Davis, 520 U.S. at 39, n. 8, 117 S.Ct. 1040.

[14] [15] The doctrine of equivalents prohibits competitors from defeating patent rights through insubstantial variations of patented matters. An accused device infringes under the doctrine of equivalents "if it performs substantially the same function in substantially the same way to obtain the same result." Graver Tank & Mfg. Co. v. Linde Air Prods., Co., 339 U.S. 605, 608, 70 S.Ct. 854, 94 L.Ed. 1097 (1950) (citation and internal quotation omitted).

[16] As the Supreme Court has noted, "the doctrine of equivalents, when applied broadly, conflicts with the definitional and public-notice functions of the statutory claiming requirement." Hilton Davis, 520 U.S. at 29, 117 S.Ct. 1040. Prosecution history estoppel provides a limitation on this potential abuse. "The essence of prosecution estoppel is that a patentee should not be able to obtain, through litigation, coverage of subject matter relinquished during prosecution." Haynes Int'l, Inc. v. Jessop Steel Co., 8 F.3d 1573, 1577 (Fed.Cir.1993). "The estoppel may result from matter surrendered as a result of amendments to overcome patentability rejections or as a result of argument to secure allowance of a claim." Cybor Corp. v. FAS Techs., 138 F.3d 1448, 1460 (Fed.Cir.1998) (internal citations omitted). "Arguments made during the prosecution of a patent application are given the same weight as claim amendments." Elkay Mfg. Co. v. Ebco Mfg. Co., 192 F.3d 973, 979 (Fed.Cir.1999).

[17] Consistent with the purposes of the patent laws discussed previously, "[t]he legal standard for determining what subject matter was relinquished is an objective one, measured from the vantage point of what a competitor was reasonably entitled to conclude, from the prosecution history, that the applicant gave up to procure issuance of the patent." Haynes Int'l, 8 F.3d at 1576 (citation omitted). *See also* Augustine Med., Inc. v. Gaymar Indus., Inc., 181 F.3d 1291, 1298 (Fed.Cir.1999). In essence, a potential competitor is entitled to fair notice of what will infringe a patent under the doctrine of equivalents, as well as literally.

[18] Accordingly, the prosecution history must be looked at as a whole. Bayer AG v. Elan Pharm. Research Corp., 212 F.3d 1241, 1252 (Fed.Cir.2000); Pharmacia & Upjohn Co. v. Mylan Pharms., Inc., 170 F.3d

1373, 1376 (Fed.Cir.1999); Elkay, 192 F.3d at 979. When, as with the '567 Patent, "multiple patents derive from the same initial application, the prosecution history regarding a claim limitation in any patent that has issued applies with equal force to subsequently issued patents *that contain the same claim limitation*." Elkay, 192 F.3d at 980 (emphasis added and citation omitted). *See also* American Permahedge, 105 F.3d at 1446; Jonsson v. The Stanley Works, 903 F.2d 812, 818 (Fed.Cir.1990).

[19] Finally with regard to the generally applicable principles, the doctrine of equivalents must be applied not only to each discrete claim, but also to the individual elements of each claim, rather than the invention as a whole that each claim describes. Hilton Davis, 520 U.S. at 29, 117 S.Ct. 1040. Thus, it is possible that prosecution history estoppel will operate to bar a finding of equivalents on some, but not all, disputed claims.

[20] In the instant case, prosecution history estoppel bars Berlex's assertion of alleged infringement based on the doctrine of equivalents of Claims 1, 40, 87, and 90 because of arguments and amendments made after the initial, 1982 application, which was not allowed. As set forth below, after their original claims were rejected by the Examiner, the applicants argued that their invention was patentably distinct because using a single DNA construct with a human interferon gene and a selectable marker generated an unexpected, material improvement over unlinked co-transformation. They also amended their claims to require the operable linkage of the interferon gene and the selectable marker on a single DNA construct. These arguments and amendments prompted the PTO to issue the '843 Patent, which includes only single construct claims.

The '567 Patent is a continuation of the '843 Patent. Its single construct claims were originally rejected as obvious. Berlex did not attempt to persuade the Examiner that her analysis concerning the single construct claims was incorrect. Rather, it filed a terminal disclaimer and, as a result, the single construct claims then pending were allowed. In obtaining allowance of those single construct claims, Berlex did not communicate to the Examiner or any other person skilled in the art that it was seeking to acquire any right to prevent devices or processes involving multiple DNA constructs-matters the inventors had distinguished in order to obtain the parent '843 Patent.

Berlex did subsequently attempt to obtain allowance of what it calls its cell and method claims. In doing so, it contended that they did not depend on the use of a single construct or linked transformation. Berlex did not assert that the previously allowed claims expressly referring to a single DNA construct now at issue were not dependent on the use of that construct. In any event, the Examiner was not persuaded that Berlex was entitled to a patent for any claims that included more than a single construct. Thus, in her Reasons for Allowance she stated that the claims allowed involved a DNA construct including an interferon gene and a DHFR marker gene.

In these circumstances, a person skilled in the art would view the prosecution history as communicating that the inventors had relinquished any claims to transformation accomplished through the use of multiple DNA constructs in order to obtain the '843 Patent and in connection with obtaining the '567 Patent had failed to acquire any right that did not include the use of a single DNA construct. The specific portions of the prosecution history on which this conclusion is based include the following.

In 1982, when the inventors applied for what emerged as the '843 Patent, every claim pertaining to transformation recited "a DNA construct" that included an interferon gene and a selectable marker gene. Bassett Aff. Ex. 4, at 23-26. The Examiner rejected these claims as anticipated and obvious in light of the

prior art. Id. at 45-48.

In 1984, the inventors made an argument and offered an amendment, each of which were material to the issuance of the '843 Patent. To overcome the Examiner's rejection and to avoid the prior art, the applicants amended the claims to require a "linkage" of the interferon and selectable marker genes on the same plasmid. They argued that this linkage generatedthe "unexpected and advantageous results" disclosed in the application. Id. at 82. More specifically, the inventors claimed that the use of a single DNA construct resulted in high levels of expression of human interferon without contamination of hamster interferon, and without human interferon toxicity to CHO cells. Id. at 81-82. They wrote:

These unexpected and advantageous results were accomplished by linking the interferon gene with the gene containing the selectable marker on a *single* DNA construct so that coamplification of the genes occurred. In the prior art, co-transformation was generally used, wherein two plasmids with the separate genes were cotransformed into the host. Thus, the instant DNA construct differs from what was done previously, and the results obtained on transforming the host with this construct were totally surprising.

Id. at 82 (emphasis in original).

Moreover, the applicants distinguished the prior art by emphasizing the single DNA construct configuration. They asserted that Axel's work and patents were distinguishable because the Axel process:

involves *co-transformation* where two separate DNA constructs with *unlinked* genes are integrated into the plasmid. In contrast, applicants' process deals with *coamplification* where the interferon gene and selectable marker gene are *linked* on the same DNA construct.

Id. at 83 (emphasis in original).

In addition, the applicants amended their claims to require linkage of the interferon gene and the selectable marker gene on a single construct. As they wrote:

Claim 1 has also been amended to include the word "linkage" to emphasize that *one* DNA construct contains *both* the selectable marker gene and the interferon gene, as opposed to cotransformants containing *two* DNA constructs carrying the separate genes.

Id. at 82-83 (emphasis in original).

The claims of the original application, as amended, ultimately issued in 1990 as the '843 Patent. Berlex agrees that the '843 Patent is literally restricted to the use of a single DNA construct comprising both interferon and marker genes. Berlex also does not contend that Biogen infringes the '843 Patent under the doctrine of equivalents, evidently because it recognizes that any such claim is barred by prosecution history estoppel.

In 1990, the inventors filed a divisional application in order to pursue additional claims based on the '843 Patent. Bassett Aff. Ex. 6, at 9. In 1992, after acquiring the '843 Patent, Berlex filed an amendment to the pending application. Chabora Dep., Bassett Aff. Ex. 21, at 53-54; Bassett Aff. Ex. 6, at 156-65. In that amendment Berlex included claims that recited a single DNA construct and claims that made no express reference to a single DNA construct. Id. at 156-64.

For example, Claim 29, which emerged in the '567 Patent as Claim 1, referred to "A DNA construct" with an interferon gene, but did not mention a selectable marker gene. Claim 29 read:

A DNA construct for expression in a Chinese hamster ovary cell or progeny thereof comprising a human interferon gene, said construct being effective for transcription and translation of said gene when introduced into a Chinese hamster ovary cell or progeny thereof.

Id. at 156.

In support of this Application, Berlex wrote:

The foregoing claims are being added to cure an inadvertent oversight during ancestor prosecution leading to U.S. Patent 4,966,843 .... In this regard, it is noted that *all claims of this application are of a scope different from that of each claim of '843*.

The oversight cured above involves the unnecessary language in the '843 claims concerning prokaryotic cell nucleotide sequences and selectable marker-related sequences. Whereas such sequences are useful in various cloning experiments and procedures, they clearly are not necessary to a prime aspect of '843, i.e., "production in Chinese hamster ovary cells" .... [I]t is important that the claims reflect this nonobvious scope. *Otherwise, infringers might attempt to avoid the literal scope of the claims, e.g., by simply preparing and/or using DNA constructs which omit components unnecessary for patentability ....*

Id. at 164 (emphasis added).

Notably, Berlex did not state that it was seeking patent protection for the production of interferon by placing interferon genes and marker genes on separate DNA constructs. Rather, it emphasized "sequences" and suggested that infringers might attempt to avoid the literal scope of the '843 Patent by using "DNA constructs which omit components unnecessary for patentability." Berlex did not clearly express concern that potential competitors would impermissibly use multiple DNA constructs to achieve transformation.

The Examiner evidently interpreted Berlex's statements as a person skilled in the art, familiar with the history of the '843 Patent, would interpret them. She viewed the claims as an effort to delete the requirement of a selectable marker gene and replace it with functionally equivalent language requiring that the single DNA construct be effective for producing interferon.

Therefore, in October 1992, the Examiner rejected all of the proposed new claims as unpatentable in light of the '843 Patent under the doctrine of obvious-type double patenting. Id. at 175. She wrote:

Although the conflicting claims are not identical, they are not patentably distinct from each other. In the parent patent, the claims recite the DNA construct by listing each element of the vector construct. The instant application seeks to remove the detailed language of the construct elements, and replaces it with functional language. *This functional language effectively limits the claims to the vector construct of the '843 application. The DNA construct, either described by its physical elements or by its function, is the same in the prior patent and the instant application*. Therefore, it would be obvious from the patent, which describes the functional characteristics of the vector in the specification, to arrive at the vector claimed in the instant application.

Id. at 175-76 (emphasis added).

By basing her rejection on "obviousness-type double patenting," the Examiner was communicating that she did not understand the claimed subject matter to be distinct from the inventions protected by the '843 Patent. *See* In re Berg, 140 F.3d at 1431. As her statement clearly reflects, among other things, the Examiner did not interpret Claim 29 as an effort to obtain protection for a process of co-transformation using multiple DNA constructs.

Berlex did not initially dispute the Examiner's assessment. Rather, on April 16, 1993, it filed a terminal disclaimer, which would cause the patent for which it was applying to expire with the expiration of the '843 Patent. Bassett Aff. Ex. 6, at 185.

Based on the terminal disclaimer, on October 19, 1993, the Examiner held claims 29 through 46, which included most of the single construct claims then pending, allowable over the prior art. Id. at 193-95, 200. She again rejected the remaining claims, which Berlex characterizes as its cell and method claims. Id.

The filing of the terminal disclaimer is not itself evidence that Berlex relinquished the claim of infringement under the doctrine of equivalents that it is now asserting. *See* Quad Environmental Techs. Corp. v. Union Sanitary Dist., 946 F.2d 870, 874 (Fed.Cir.1991). "[T]he filing of a terminal disclaimer simply serves the statutoryfunction of removing the rejection of double patenting, and raises neither presumption nor estoppel on the merits of the rejection." *Id*. It is, however, relevant that as of October 19, 1993, the claims expressly referring to a single construct had been allowed because this fact would contribute to causing a person skilled in the art to understand that Berlex's subsequent statements related only to the claims that the Examiner had again rejected.

Berlex subsequently made another attempt to get its remaining claims allowed. On September 14, 1994, its attorney met with the Examiner. Bassett Aff. Ex. 6, at 200. As a result of that meeting the Examiner initially described the agreement reached by writing, "Claims will be narrowed." *Id*. At the request of Berlex's attorney, she amended this comment to state, "Construct claims will be narrowed to include DHFR marker." *Id*.

When it is not clear from the prosecution record why an amendment was made, there is a presumption that it was required for patentability. Hilton Davis, 520 U.S. at 33, 117 S.Ct. 1040. Here, however, the claims characterized by Berlex as "construct claims" had already been allowed. Thus, the amendment that had been agreed to was not necessary to the patentability of those claims. Read in the context of the prior prosecution history, however, the Examiner's description of the agreement would communicate to a person skilled in the art that Berlex had represented that there were at least some claims that required a single construct to be patentable, and that those claims would be amended to require that DHFR be the marker gene linked to the interferon gene on that single construct.

On September 21, 1994, Berlex made another submission to the Examiner. First, it filed an amendment modifying the construct claims that had already been allowed as a result of the terminal disclaimer to require a DHFR marker genes as well as an interferon gene. *Id*. at 201-11.

In addition, Berlex made several arguments that it now emphasizes. Specifically, Berlex wrote that:

The claims continue to reflect the pioneering invention of the first expression of interferon (IFN) genes in Chinese hamster ovary (CHO) cells. *Id*. at 213.

* * * * * *

[The] broad method claims, such as 51 and 71, and CHO cell claims, such as 104 and 108 [are one example of] The broadest scopes of the method and CHO cell classes of claims. *Id*. at 214.

* * * * * *

As mentioned above, the claimed invention represents the first expression of human interferons in CHO cells ... Overall, the claims are non-obvious, e.g., because the field was so unpredictable that even if a skilled worker had been generally motivated to attempt to express human IFN's in CHO cells, there would have been no reasonable expectation for success. *Id*. at 217.

* * * * * *

Where the record of this application differs from that of ancestor prosecution ... it is the current record which is relevant. *Id*. at 222-23.

* * * * * *

It is not relevant whether the Axel et al. prior art patent disclosures of record actually employ only unlinked cotransformed genes in their work. (Axel et al. do generically disclose linked such genes ....) *Patentablility and breadth of the current claims reflect the non-obviousness of the first expression of human IFN in CHO cells and do not depend on any particular nucleic acid construct configuration*. *Id*. at 223 (emphasis added).

Berlex asserts that these "statements unambigously alert[ed] the Examiner (and any competitor reviewing the '567 prosecutionhistory) to the fact that broad subject matter outside the 'single DNA construct' covered by the '843 Patent claims was being claimed." Berlex's Opp'n to Biogen's Mot. for Summ. J. of Non-Infringement of "Single Construct" Claims of the '567 Patent, at 14. This contention, however, is incorrect.

First, the prosecution history estoppel analysis must proceed claim by claim and element by element. Hilton Davis, 520 U.S. at 40, 117 S.Ct. 1040 ("[t]he determination of equivalence should be applied as an objective inquiry on an element-by-element basis."). A person skilled in the art would view Berlex's reference to "the current claims" and its other comments as being addressed to the cell and method claims that had been rejected, rather than the construct claims which had already been allowed.

Second, a person skilled in the art seeking to determine what was protected and what was prohibited under the doctrine of equivalents after the '567 Patent was issued would also consider the Examiner's subsequent Reasons for Allowance. As described previously, she wrote in allowing all of the claims:

Applicants[’] claims are directed to a DNA construct comprising a vector, an interferon gene, and a dhfr marker gene. The construct is expressed in CHO cells. The instant claims are similar to the claims in parent Patent 4,966,843 ('843), however the instant claims recite the marker gene to be dhfr, whereas the '843 claims do not. Since a terminal disclaimer has been filed over the '843 claims, the instant claims are held allowable.

Id. at 336.

After reading the Reasons for Allowance, the last entry in the public file, a person skilled in the art would understand the following. In order to obtain the '843 Patent the inventors strenuously argued the distinctive value of utilizing a single DNA construct and amended their application to require the operable linkage of an interferon gene and a selectable marker gene on a single construct. Berlex did not communicate to the Examiner that it was abandoning this position before the claims of the '567 Patent which referred expressly to *a* DNA construct were allowed in 1993. Berlex did subsequently attempt to persuade the Examiner to allow what it now characterizes as cell and method claims that did not depend on the use of a single DNA construct, but failed. Thus, the Examiner viewed the distinction between the use of single and multiple DNA constructs to be material to the patentability of all of the claims and did not allow any claims which protected more than the use of a single DNA construct. *See* Elkay, 192 F.3d at 979 (assessing materiality of a statement for prosecution estoppel purposes based on Examiner's response to it).

Accordingly, with regard to the construct claims now at issue, the court finds that a person skilled in the art reading the prosecution history would conclude that the inventors of the '843 Patent relinquished any right to argue that the use of multiple, separate constructs to introduce interferon and DHFR into CHO cells is the equivalent of the use of a single construct. In seeking the '567 Patent Berlex did not communicate to the Examiner or the public that it was attempting to broaden the claims referring to a single construct to cover the use of multiple constructs. Rather, it further limited its construct claims to the use of DHFR as the marker gene. Thus, the court finds that Berlex is estopped from now asserting the position its predecessors relinquished to obtain the '843 Patent.

Berlex is, therefore, barred by the prosecution history from attempting to prove that Claims 1, 40, 87, and 90 and their dependent claims infringe the '567 Patent based on the doctrine of equivalents. In view of the amendment providing for "operable linkage" concerning certain of the claims in the '843 Patent, this conclusion is even stronger with regard to Claims 46, 73-77, and 81-83, dependent claims in the '567 Patent that include the "operable linkage" limitation. '567 Patent, at 29:38-40, 30:61-31:4, and 31:12-19.

Because Biogen is entitled to summary judgment on Berlex's claim of infringement of the '567 Patent under the doctrine of equivalents based on prosecution history estoppel, the court is not addressing the merits of the second issue presented, whether the "all elements" test is met. The law in this area is not now clear because the Court of Appeals for the Federal Circuit withdrew its most recent, significant decision concerning the "all elements" rule and has held a hearing en banc to clarify the meaning of *Hilton Davis* ' "requirement that the doctrine of equivalents [ ] not [be] allowed such broad play as to eliminate [an] element in its entirety." *See* Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co., 187 F.3d 1381 (Fed.Cir.1999) (quoting Hilton Davis, 520 U.S. at 29, 117 S.Ct. 1040). Because it is not necessary to decide the instant motion, the court will not now attempt to anticipate the results of that rehearing.

VI. BERLEX'S MOTION FOR SUMMARY JUDGMENT CONCERNING LITERAL INFRINGEMENT OF THE '779 PATENT

[21] Berlex has moved for summary judgment on its contention that the production of Avonex by Biogen literally infringes Berlex's '779 Patent. The parties agree that with regard to the issue of literal infringement there are no material facts in dispute. Therefore, once the disputed claims are construed, the entry of summary judgment is appropriate. Athletic Alternatives, 73 F.3d at 1578.

For the reasons described below, the court concludes that Biogen's proposed claim construction is correct. Therefore, the production of Avonex does not literally infringe the '779 Patent.

In August 1994, Berlex filed an application, based on the specification for the '843 and '567 Patents, which eventually led to the issuance of the '779 Patent. Bassett Aff. Ex. 7, at 1. In 1996, the pending lawsuits concerning the '567 Patent were filed. *See* Bg's Compl.; Blx's First Compl. In October 1996, Berlex's then pending claims were rejected by the Examiner as obvious over the prior art, the Axel '216 Patent. Bassett Aff. Ex. 7, at 112, 115-16.

On March 27, 1997, Berlex cancelled all of its pending claims and submitted a new set of claims that emerged in 1998 as the '779 Patent. Id. at 121-25. The '779 Patent includes a single independent claim, the construction of which resolves all issues concerning the literal infringement of the '779 Patent.FN20

FN20. Biogen asserts that if Berlex's construction of Claim 1 were adopted, the court would also have to decide whether the '779 Patent is limited to transformation of CHO cells accomplished by the use of a single DNA construct. Mar. 10, 2000 Tr. at 72. Because the court finds that Biogen's proposed construction is correct, this issue is moot.

That claim, Claim 1, recites:

1. A CHO cell culture composition comprising (a) CHO cells transformed with DNA encoding human IFN-(beta), or progeny thereof, and (b) medium comprising IFN-(beta) produced by expression of said DNA, said culture composition directly resulting from secretion of said IFN-(beta) from said CHO cells and wherein the amount of said IFN-(beta) is 150,000-600,000 IU/ml of medium.

'779 Patent, Bassett Aff. Ex. 3, 28:6-12. Berlex characterizes this as a "product" or "composition" claim, as distinct from its construct, cell and method claims.

In an effort to obtain fast allowance of its new claims, Berlex represented to the PTO that it was placing an upper limit on the literal scope of Claim 1 and its dependent claims. More specifically, on March 27, 1997, Berlex stated:

[T]he achievement by this invention of amounts of (beta)-interferon as high as 600,000 IU/ml is strikingly superior and unexpected.... There is nothing in any of the prior art which would lead a skilled worker to have expected this result.

* * * * * *

The only reason applicants have chosen to place an upper limit on the literal scope is to enhance a fast allowance by minimizing potential issues. In fact, a claim scope which literally includes values higher than 600,000 IU/ml, is clearly justified .... As for the lower limit, in view of Paragraph No. 9[of] the accompanying declaration by Dr. Jan Vilcek, it can be seen that the value of 150,000 IU is although precise, somewhat arbitrary. Thus, a scope of equivalents less than this value is warranted.

Bassett Aff. Ex. 7, at 129-30 (emphasis added).

The foregoing statements were made in an evident effort to avoid the holding of cases such as In re Fisher, 57 C.C.P.A. 1099, 427 F.2d 833, 839 (1970), which disallowed "open ended" product claims, with no upper limit, because the specification did not enable a person skilled in the art to achieve a higher potency than had been achieved by the applicant. Berlex's representations served their intended purpose. Less than three months later, on June 10, 1997, the new claims were allowed. Bassett Aff. Ex. 7, at 171-72.

The Court of Appeals for the Federal Circuit has held that:

An applicant should not be able deliberately to narrow the scope of examination to avoid during prosecution scrutiny by the PTO of subject matter with the objective of more quickly obtaining a patent (or avoiding the risk of an estoppel), and then obtain in court, either literally or under the doctrine of equivalents, a scope of protection which encompasses that subject matter.

Genentech, Inc. v. The Wellcome Found. Ltd., 29 F.3d 1555, 1564 (Fed.Cir.1994). That is, however, precisely what Berlex is attempting to do with regard to the '779 Patent.

It is undisputed that in the process of producing Avonex, Biogen achieves concentration levels of interferon substantially in excess of 1,000,000 IU/ml. Mar. 10, 2000 Tr. at 41. More specifically, it has been stipulated that the nine bioassays performed for Biogen by Dr. Wendy Jones on Avonex samples are reliable. Stipulation (Jan. 14, 2000). These nine tests resulted in the measurement of 1,200,000 IU/ml two times, 1,500,000 IU/ml six times, and 1,600,000 IU/ml one time. Id.

At intermediate stages of the Biogen process, however, the concentration of interferon passes through the 150,000-600,000 IU/ml range. Letter from E.J. Brown to D.J. Nossel (Feb. 19, 1999), Brooks Rule 56(f) Decl. Ex. 18. Indeed, if, as required by Claim 1, the culture composition directly results from the secretion of interferon by transformed CHO cells, the composition must pass through the 150,000 to 600,000 IU/ml range to achieve higher levels, as a bucket being filled with a hose must contain a quart of water before it can contain a gallon.FN21

FN21. Biogen originally submitted the affidavit of Dr. Dane Zabriskie to establish that Biogen substantially exceeds interferon concentrations of more than 1,000,000 IU/ml at the end of its process. Aff. of Dane Zabriskie in Supp. of Bg.'s Mots. for Summ. J. ("Zabriskie Aff.") para. 19. In the course of explaining this statement, Dr. Zabriskie stated that in the cell culturing process the concentration of interferon starts at zero and increases as the cells grow in the medium until the maximum concentration in the container being utilized is reached. Id. at para.para. 13, 14. Berlex moved to strike Dr. Zabriskie's affidavit, primarily based on the claim that he lacked personal knowledge of the concentration levels at the end of the Biogen process. [Revised] Mem. in Supp. of Berlex's Mot. to Strike the Aff. of Dr. Dane Zabriskie at 4-12. Biogen withdrew Dr. Zabriskie's affidavit. Nov. 18, 1999 Tr. at 180. Therefore, the court has not relied on that affidavit.

However, Biogen has continued to argue that if, as Claim 1 provides, the culture composition is produced directly from the secretion of interferon from transformed CHO cells, that composition must as a practical matter pass through the range below 150,000 IU/ml before it achieves that level. Mar. 10, 2000 Tr. at 43, 61. The court understands this contention to be correct and, more significantly for present purposes, not placed in genuine dispute by Berlex.

Berlex has not stated that it disputes Biogen's assertion that if the composition is produced by the direct secretion of interferon from transformed CHO cells it must pass through lower levels before achieving a concentration of 150,000 IU/ml. Id. at 86. Nor has it identified any example of a process that has produced an interferon concentration in the 150,000-600,000 IU/ml range without passing through lower ranges. *See* id. at 110.

Berlex does point to the testimony of Dr. Susan Goelz of Biogen. Id. at 28-29. Dr. Goelz testified that, "there might be some methods that [Biogen] could use" to produce Avonex in which the interferon concentration was always in excess of 600,000 IU/ml. Goelz Dep., 4th Bursor Decl., Ex. 1, at 564-66. However, she said she did not know if this would be possible. Id. at 566. For two reasons Dr. Goelz's testimony would not be admissible at trial to prove that concentrations of interferon above 600,000 IU/ml could be achieved by the direct secretion from transformed CHO cells without going through lower ranges. First, the questions Dr. Goelz was asked were not limited to the production of a composition resulting directly from the secretion of interferon by transformed CHO cells. Id. at 564-66. Thus, she expressed no opinion on the relevant question. Second, Dr. Goelz did not express any opinion with the legally required degree of reasonable certainty. *See* Goldstein v. Kelleher, 728 F.2d 32, 40 (1st Cir.1984); General Elec. Co. v. Joiner, 522 U.S. 136, 146, 118 S.Ct. 512, 139 L.Ed.2d 508 (1997); Licciardi v. TIG Ins. Group, 140 F.3d 357, 365 (1st Cir.1998). It is axiomatic that inadmissible evidence may not be considered in determining whether there is a genuine dispute concerning a material fact when deciding a motion for summary judgment. *See* Fed.R.Civ.P. 56(e) ("affidavits ... shall set forth such facts as would be admissible in evidence ...."); Scosche Indus., Inc. v. Visor Gear, Inc., 121 F.3d 675, 681 (Fed.Cir.1997) (evidence must be admissible at trial in order to be properly considered when deciding a summary judgment motion). Therefore, the crucial question is whether, as Berlex contends, Claim 1 covers an interferon culture composition which at any time passes through the 150,000-600,00 IU/ml range or whether, as Biogen asserts, it includes only compositions which are in this range after confluence and superinduction-that is, after the transformed cells reach their maximum density on the plate or in the roller bottle being utilized and are chemically stimulated to produce interferon. The generally applicable principles concerning claim construction described in s. IV, *supra* are equally applicable here. Among other things, where, as here, a product or composition claim is being construed, "a review of the claim[ ], the specification, and the prosecution history" is necessary. Lubrizol, 64 F.3d at 1557.

In addition, even if the intrinsic evidence is clear, "it is entirely appropriate, perhaps even preferable, for a court to consult trustworthy extrinsic evidence to ensure that the claim construction it is tending to from the patent file is not inconsistent with clearly expressed, plainly apposite, and widely held understandings in the pertinent technical field." Pitney Bowes, 182 F.3d at 1309. This is because, "[t]he process of claim construction at the trial court level will often benefit from expert testimony which may (1) supply a proper technological context to understand the claims (words often have meaning only in context), (2) explain the meaning of claim terms as understood by one of skill in the art (the ultimate standard for claim meaning), and (3) help the trial court understand the patent process itself (complex prosecution histories-not to mention specifications-are not familiar to most trial courts)." *Id*. at 1314 (Rader, J., concurring) (internal citations omitted). The court may not, however, "rely on extrinsic evidence in claim construction to contradict the meaning of claims discernable from thoughtful examination of the claims, the written description, and the prosecution history-the intrinsic evidence." *Id*. at 1308.

[22] In the context of construing the '779 Patent, it is also important to recognize that a claim should not be interpreted in a manner which eliminates a limitation recited in that claim. Unique Concepts, Inc. v. Brown,

939 F.2d 1558, 1562 (Fed.Cir.1991).

Claim 1 includes words which require clarification by reference to at least the specification and prosecution history, and provide a "textual reference in the actual language of the claim with which to associate [the] proffered claimed construction" of each party. Johnson Worldwide, 175 F.3d at 990. Specifically, Claim 1 provides patent protection for a culture composition in which the "amount" of interferon "is 150,000-600,00 IU/ml of medium." It is not clear from the language of the claim alone, however, when the amount of interferon is to be measured. Rather, the language of the claim is compatible with the contrary constructions advocated by each of the parties.

As set forth below, the specification and prosecution history each support the construction, proposed by Biogen, that the amount of interferon is to be measured after confluence and superinduction, which is essentially the end of the process of producing interferon. This interpretation of Claim 1 is reinforced by the trustworthy extrinsic evidence, rather than contradicted by it.

The pertinent portion of the '779 Patent specification is Table 1, which is the only express disclosure in the specification of the interferon concentrations achieved in CHO cell culture compositions. Table 1, Bassett Aff. Ex. 3; Ex. C hereto. There is only one experiment described in Table 1 in which an interferon concentration of as high as 150,000-600,00 IU/ml was achieved. Id. The Table explicitly explains that concentration was achieved only after confluence had occurred and superinduction was used to stimulate the production of interferon. *Id*. n. 3.

The foregoing indicates that Table 1 would communicate to a person ordinarily skilled in the art that Claim 1, and its dependent claims, are each directed to compositions achieved after confluence and superinduction. *See* Morehouse Indus., 143 F.3d at 1463 (interpreting "driving surface" in light of the disclosed examples in the specification as limited to flat surfaces although there was no claim language expressly reciting that limitation); ATD Corp., 159 F.3d at 542 (interpreting "embossments" in light of the disclosed examples in the specification to require depressions or bumps sufficient to separate adjacent layers, although there was no claim language to that effect).

The trustworthy extrinsic evidence reinforces the conclusion that a person skilled in the art would understand Table 1, and the claims of the '779 patent, to be limited to compositions measured after confluence and superinduction, the end of the culturing process. More specifically, at their depositions, one of the named inventors of the Berlex patents, Dr. Ringold, and Berlex's experts each read Table 1 and promptly recognized that an interferon level of 150,000-600,00 IU/ml had been achieved only after confluence and superinduction. Ringold Dep., Bassett Aff. Ex. 11, at 869-72; Vilcek Dep., Bassett Aff. Ex. 15, at 754, 784; Pitha-Rowe Dep., Bassett Aff. Ex. 14, at 480-82, 509-14, 644-45; Trahey Dep., Bassett Aff. Ex. 13, at 209-10.

In addition, Dr. Silverstein, one of the named inventors of the Axel '216 Patent, submitted an affidavit that directly addresses the question at issue. Declaration of Dr. Saul J. Silverstein (Apr. 29, 1999) ("1st Silverstein Decl."), para.para. 4, 51-54. Dr. Silverstein states that, in his experience, scientists reading papers that report concentration levels of protein expression generally understand them to be the ultimate levels obtained in the experiments being reported. Id. para. 51. With regard to the '779 Patent, he asserts that in view of the fact that the specification indicates that an interferon concentration of 150,000-600,000 IU/ml was achieved only after confluence and superinduction, a person skilled in the art "would understand that the claimed range was an ultimate yield, measured after superinducing the IFN-(beta) gene at the end of the

CHO cell culturing process." Id. para. 53. Berlex has not submitted any expert evidence to contradict this opinion.

The prosecution history is also consistent with Biogen's proffered construction of Claim 1. Berlex emphasizes that in presenting its claims it told the Examiner that:

The values recited in the claims are in reference to the bioassay for antiviral activity described in Table 1 of the application. *These values are measurable from samples removed at any time from the claimed culture composition*.

Bassett Aff. Ex. 7, at 126; Brooks Decl. Ex. 21, at 123 (emphasis added). Berlex contends that this statement communicated to the Examiner, as it would to anyone skilled in the art, that if a competing product went through the claimed range "at any time," it would infringe what became the '779 Patent. *See, e.g.,* Mar. 10, 2000 Tr. at 31-33.

The quoted language does not, however, directly address competitors' products. Rather, it addresses the bioassays reported in Table 1. If the statement quoted is interpreted to represent that a concentration of 150,000-600,000 IU/ml would be found in the composition reported if it were measured at any time, including at the inception of the superinduced secretion process, it is untrue because a composition that results directly from the secretion of interferon by transformed CHO cells must go through lower concentrations before achieving a concentration of 150,000-600,000 IU/ml. The composition reported in Table 1 would only measure 150,000-600,000 IU/ml at any time after confluence and superinduction.

Thus, the language in the prosecution history on which Berlex relies most heavily actually tends to support Biogen's proposed claim construction. More significant is the representation Berlex made which was quoted earlier, that it was placing "an upper limit on the literal scope ... to enhance a fast allowance by minimizing potential issues." Bassett Aff. Ex. 7, at 129-30. This representation was made in the midst of the instant litigation, which Berlex had not yet disclosed to the Examiner. Id. at 189-94. As indicated earlier, it served its intended purpose and Berlex's claims were promptly allowed. Id. at 171-72.

The court concludes that the Examiner, like any person skilled in the art, understood Berlex to be representing that it would not assert that its claims were literally infringed by a product which achieved an ultimate concentration level in excess of 150,000-600,000 IU/ml. Thus, among other things, the Examiner did not have to decide whether Berlex was seeking protection for the sort of open ended claims not enabled by the specification which were disallowed in In re Fisher, 427 F.2d at 839.

Accordingly, Berlex's current contention that the '779 Patent is literally infringed by Biogen is the type of conduct condemned by the Court of Appeals for the Federal Circuit in Genentech, 29 F.3d at 1564: a deliberate narrowing of claims to avoid scrutiny by the PTO to obtain quick allowance and a subsequent effort to acquire in court the relinquished subject matter. *See also* Unique Concepts, 939 F.2d at 1562 (proposed claim construction would inappropriately "encourage an applicant to escape examination of a more broadly-claimed invention by filing narrow claims and then, after grant, asserting a broader scope of the claims based on a statement in the specification of an alternative never presented in the claims for examination").

Moreover, interpreting the '779 Patent as Berlex advocates would violate two canons of claim construction. It would effectively eliminate an express limitation in Claim 1 and its dependent claims. It would also render

the patent invalid because the specification is insufficient to satisfy the requirements of 35 U.S.C. s. 112 if the claims cover compositions with ultimate concentrations in excess of 150,000-600,000 IU/ml.

As indicated earlier, "[t]o literally infringe, the accused [product] must contain every limitation of the asserted claim." Texas Instruments, Inc. v. Cypress Semiconductor Corp. (" Cypress Semiconductor "), 90 F.3d 1558, 1563 (Fed.Cir.1996). Generally, claims should not be interpreted to read a limitation out of a claim. Ethicon Endo-Surgery, Inc. v. United States Surgical Corp., 93 F.3d 1572, 1581 (Fed.Cir.1996). Rather, courts "must give meaning to all the words in [the] claims." Lubrizol, 64 F.3d at 1557.

Berlex contends that its proposed construction of the '779 Patent would not eliminate the express upper limit of 600,000 IU/ml because if a composition were measured and found to have a concentration in excess of 600,000 IU/ml it would not literally infringe Berlex's patent. Mar. 10, 2000 Tr. at 82. However, as described earlier, any composition directly resulting from the secretion of interferon by transformed CHO cells must go through 150,000-600,000 IU/ml level to achieve a higher concentration. Therefore, if Berlex's proposed construction of the '779 Patent were adopted any measurement in excess of 600,000 IU/ml would be proof that the patent had been infringed in the course of creating that composition. Thus, the 600,000 IU/ml limitation would, as a practical matter, be read out of the patent. Such a construction is inappropriate. Ethicon Endo-Surgery, 93 F.3d at 1582; Texas Instruments, Inc. v. International Trade Comm'n, 988 F.2d at 1171; Unique Concepts, 939 F.2d at 1562.

Berlex's proposed construction of the '779 Patent is also inconsistent with the principle that "claims are not properly construed to have a meaning or scope that would lead to their invalidity for failure to satisfy the requirements of patentability." Wang, 197 F.3d at 1383. The only product that is adequately described and enabled FN22 in the specification of the '779 Patent is a composition with an interferon concentration of up to 600,000 IU/ml achieved after confluence and superinduction. As the Court of Appeals for the Federal Circuit has held, while a single embodiment may be sufficient to provide broad enablement in cases involving predictable factors, such as familiar mechanical or electrical elements, the scope of enablement is in less when unpredictable factors are involved. In re Fisher, 427 F.2d at 838. Thus, in *In re Fisher,* the Federal Circuit held that an open ended product claim, with no upper limit, was insufficiently supported and, therefore, not in compliance with 35 U.S.C. s. 112. *Id.* at 839. Berlex's proposed construction of the '779 Patent would suffer from the same infirmity. Accordingly, the reasonable, narrower construction advocated by Biogen is more appropriate. Wang, 197 F.3d at 1383.

FN22. With regard to enablement, 35 U.S.C. s. 112, paragraph 1 states:
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, and shall set forth the best mode contemplated by the inventor of carrying out his invention.

[23] Finally, the construction proffered by Biogen is the most consistent with the vital public notice function intended to be served by the patent laws. As described earlier, 35 U.S.C. s. 112, para. 2 requires that "an inventor particularly point out and distinctly claim the subject matter of his invention." Unique Concepts, 939 F.2d at 1562. "The primary purpose of the requirement is to guard against unreasonable advantages to the patentee and disadvantages to others arising from uncertainty as to their [respective] rights." Athletic Alternatives, Inc., 73 F.3d at 1581 (internal quotations omitted). Therefore, even "[w]here there is an equal

choice between a broader and a narrower meaning of a claim, and there is an enabling disclosure that indicates that the applicant is at least entitled to a claim having the narrower meaning ... the notice function of the claim [is] best served by adopting the narrower meaning." *Id*. Although in this case the intrinsic and extrinsic evidence favor Biogen, rather than rendering the choice of proffered claim constructions equal, consideration of the public notice function of the patent laws reinforces the conclusion that Biogen's proposed construction of the '779 Patent should be deemed correct.FN23

FN23. The court understands that its construction of Claim 1 renders it identical in scope to dependent Claims 7 and 24, which expressly state that the protected cell culture was superinduced. '779 Patent, Bassett Aff. Ex. 3, 28:27-30, 29:4-7. Thus, the court initially presumed that Claim 1 was different in scope than Claims 7 and 24. Comark, 156 F.3d at 1187. However, the pertinent parts of the specification and prosecution history, discussed *supra,* rebut this presumption. Toro, 199 F.3d at 1302. Among other things, to construe Claim 1 as Berlex advocates would impermissibly broaden its scope beyond the scope of the underlying disclosure. Kraft Foods, 203 F.3d at 1368; ATD Corp., 159 F.3d at 541.

The court recognizes that, as Berlex emphasizes, Biogen's construction of the '779 Patent as protecting only compositions which have an interferon level of 150,000-600,000 IU/ml after confluence and superinduction differs from the holding that the composition claim in *Lubrizol* contained no temporal limitation. Lubrizol, 64 F.3d at 1558. In *Lubrizol,* the Court of Appeals for the Federal Circuit found that the "chemical composition [claimed] exists at the moment the ingredients are mixed together." *Id*. at 1558. It held that, "as properly interpreted, Exxon's claims are to a composition that contains the specified ingredients *at any time* from the moment at which the ingredients are mixed together." *Id*. (emphasis added).

However, this court does not understand *Lubrizol* to be a ruling that composition claims may never have a temporal limitation. Rather, *Lubrizol* reaffirms that each composition claim, like all other claims, must be construed in the context of its unique specification and prosecution history. *Id*. at 1557.

For the reasons previously stated, the specification and prosecution history of the '779 Patent indicate that its claims are subject to a temporal limitation: they cover compositions which have interferon concentrations of 150,000-600,000 IU/ml after confluence and superinduction. The trustworthy extrinsic evidence reinforces this conclusion. It is undisputed that after confluence and superinduction Biogen achieves interferon concentration levels in the 1,200,000 to 1,600,000 IU/ml range. Thus, Biogen does not literally infringe the '779 Patent.

VII. BIOGEN'S MOTION FOR SUMMARY JUDGMENT CONCERNING INFRINGEMENT OF THE '779 PATENT UNDER THE DOCTRINE OF EQUIVALENTS

[24] Biogen has moved for summary judgment on Berlex's assertion that Biogen infringes the '779 Patent under the doctrine of equivalents. Contrary to Berlex's assertion, no material fact is genuinely in dispute. Thus, the issue of equivalents is ripe to be resolved on Biogen's motion for summary judgment. Hilton Davis, 520 U.S. at 39 n. 8, 117 S.Ct. 1040; Athletic Alternatives, Inc., 73 F.3d at 1578. For the reasons set forth below, that motion is meritorious.

The standards regarding the doctrine of equivalents described in s. V, *supra,* are also applicable to the instant motion. In essence, to establish a violation under the doctrine of equivalents Berlex must establish that there is only an "insubstantial" difference between Biogen's product and the composition protected by

the '779 Patent. Graver Tank, 339 U.S. at 608, 70 S.Ct. 854. Moreover, Berlex's claim of infringement under the doctrine of equivalents may be barred by prosecution history estoppel. Haynes Int'l, 8 F.3d at 1577. As indicated earlier, "[t]he essence of prosecutionhistory estoppel is that a patentee should not be able to obtain, through litigation, coverage of subject matter relinquished during prosecution." *Id*.

In this case, Berlex's claim of infringement of the '779 Patent is barred by prosecution history estoppel. In addition, Berlex has failed to provide the evidence necessary to permit a jury to conclude that the differences between Biogen's product and the composition protected by the '779 Patent are insubstantial. *See* Cypress Semiconductor, 90 F.3d at 1566; Lear Siegler, Inc. v. Sealy Mattress Co. of Mich., Inc., 873 F.2d 1422, 1425-26 (Fed.Cir.1989).

Berlex submitted the claims that emerged as the '779 Patent to the PTO in March 1997, about ten months after this litigation commenced. Bg.'s Compl.; Bassett Aff. Ex. 7, at 121-31. The court infers that Berlex sought to have additional claims allowed in order to improve its prospects of prevailing in court. Berlex did not disclose the existence of this litigation to the Examiner before its claims were initially allowed in June 1997. Bassett Aff. Ex. 7, at 171.FN24 As described earlier, in March 1997, Berlex told the Examiner that:

FN24. Berlex informed the Examiner of this litigation in September 1997. Bassett Aff. Ex. 7, at 189. The claims were again allowed on January 5, 1998. Id. at 228. The '779 Patent issued on August 18, 1998. Bassett Aff. Ex. 3, at 1.

The only reason applicants have chosen to place a [600,000 IU/ml] upper limit on the literal scope is to enhance fast allowance by minimizing potential issues. In fact, a claim scope which literally includes values higher than 600,000 IU/ml is clearly justified.
Bassett Aff. Ex. 7, at 129-30. As a result, Berlex achieved the prompt allowance of its claims. Id. at 171-72. As also described previously, the foregoing representation communicated to the Examiner, as it would any person skilled in the art, that Berlex was relinquishing any claim that a composition that achieved an interferon concentration in excess of 600,000 IU/ml literally infringed the '779 Patent. Arguably, the language Berlex used would signal to a competitor that Berlex was reserving its right to contend that any such composition infringed the '779 Patent under the doctrine of equivalents.

The Court of Appeals for the Federal Circuit's analysis in *Genentech, supra,* is instructive on this issue. There the court found that the diverse definitions utilized in the specification reflected "either inartful drafting, a conscious attempt to create ambiguity about the scope of the claims, or a desire to claim a wide variety of materials not described or enabled in the specification." Genentech, 29 F.3d at 1564. In deciding the issue of equivalents, the court narrowly construed the claims at issue in order to "avoid[ ] the possibility of an applicant obtaining in court a scope of protection which encompasses subject matter that, through the conscious efforts of the applicant, the PTO did not examine." *Id*. As stated earlier, the court concluded that:

An applicant should not be able deliberately to narrow the scope of examination to avoid during prosecution scrutiny by the PTO of subject matter with the objective of more quickly obtaining a patent ... and then obtaining in court, *either literally or under the doctrine of equivalents,* a scope of protection which encompasses that subject matter.

Id. (emphasis added).

The reasoning of *Genentech,* is equally applicable to the instant motion. In its successful effort to have its claims allowed promptly, Berlex expressly removed from scrutiny by the PTO the scope of protection it now seeks in court. Its statement to the Examiner was artfully worded to permit Berlex to argue now that it had preserved its right to assert infringement under the doctrine of equivalents. However, as the Court of Appeals for the Federal Circuit has explained, if Berlex wanted broad patent protection, it should have sought it from the PTO. Sage Prods., Inc. v. Devon Indus., 126 F.3d 1420, 1425 (Fed.Cir.1997).

Had [Berlex] done so, then the Patent and Trademark Office (PTO) could have fulfilled its statutory role in helping ensure that exclusive rights issue only to those who have, in fact, contributed something new, useful, and unobvious. Instead, [Berlex] left the PTO with manifestly limited claims that it now seeks to expand through the doctrine of equivalents. However, as between the patentee who had a clear opportunity to negotiate broader claims but did not do so, and the public at large, it is the patentee who must bear the cost of its failure to seek protection for this foreseeable [claim].

Id.

[25] In addition, even viewed in the light most favorable to it, Berlex has failed to submit sufficient evidence to permit a reasonable factfinder to conclude that Biogen infringes the '779 Patent under the doctrine of equivalents. In order to prove infringement on the basis of equivalents, "a patentee must ... provide *particularized testimony* and linking argument as to the 'insubstantiality of the differences' between the claimed invention and the accused [product]." Cypress Semiconductor, 90 F.3d at 1567 (emphasis added). *See also* Lear Siegler, Inc., 873 F.2d at 1425. This means that there must be "testimony explicitly comparing the claimed and accused [products]." *Id.* Such particularlized testimony "must be presented on a limitation-by-limitation basis. Generalized testimony as to the overall similarity between the claims and the accused infringer's product or process will not suffice." Cypress Semiconductor, 90 F.3d at 1567.

In *Cypress Semiconductor,* the Court of Appeals for the Federal Circuit affirmed a ruling that the patentee had failed to present sufficient evidence to support a jury's finding of infringement under the doctrine of equivalents. *Id.* Two experts had addressed the issue of equivalents on behalf of the plaintiff. *Id.* However, the "overwhelming majority" of one expert's testimony "was solicited for purposes of establishing literal infringement." *Id.* His testimony that the conductors and processes being compared were the "same" and "performed the same function" was deemed to be "merely generalized testimony as to overall similarity," rather than the required "particularized testimony" regarding equivalents. *Id.* at 1567-68. The second expert's testimony was also found to be inadequate because he testified only in a "conclusive fashion," stating that the *Graver Tank* test was met, without explaining the reasons for his opinion. *Id.* at 1568.

In the instant case, Berlex identified three expert witnesses, each of whom submitted a report concerning his or her opinions and testified at a deposition. Mar. 10, 2000 Tr. at 74-78, 108. No expert expressed an opinion in his or her report concerning whether Biogen infringed the '779 Patent under the doctrine of equivalents. Id. Nor did Berlex question any of its experts on this subject at his or her deposition. Id.; Hiscott Dep., Bassett Aff. Ex.71, at 535-36. Thus, Berlex did not elicit from its experts any of the particularized testimony that is required to prove infringement under the doctrine of equivalents.

In its effort to identify sufficient evidence to survive Biogen's motion for summary judgment on equivalents, Berlex relies primarily on the responses provided by one of its experts, Dr. Vilcek, to questions asked at his deposition by Biogen. Mar. 10, 2000 Tr. at 103-04. Dr. Vilcek expressly stated that he had not formed an opinion concerning whether Biogen infringes the claims of the '779 Patent under the doctrine of equivalents.

Vilcek Dep. at 733, Letter from W.F. Lee and R.W. Clary to Judge Wolf (Aug. 10, 2000). He testified that he had not considered that issue. Id. Subsequently, in response to several questions from Biogen's counsel, Dr. Vilcekstated that a person skilled in the art would consider an interferon concentration of 2,000,000 IU/ml to be "different" than a composition with 600,000 IU/ml, but in his opinion an interferon composition of 1,000,000 IU/ml would "probably not" be different. Vilcek Dep., Bursor Decl. Ex. 18, at 1176-77. Dr. Vilcek did not explain his qualified, conclusory opinion. *See* id. Nor did he state whether he considered interferon concentrations in the 1,200,000 to 1,600,000 IU/ml range, which were found in Avonex samples by Dr. Jones, to be substantially different than the product protected by the '779 Patent. *See* id.; Stipulation (Jan. 14, 2000). FN25

FN25. The court understands that Dr. Vilcek's deposition was taken before Berlex received and stipulated to the reliability of the interferon concentrations found in Avonex samples by Dr. Jones. In view of the fact that Berlex elicited no particularized evidence from its experts on the instant issue of equivalents before receiving Dr. Jones' results, and made no effort to supplement its submissions after stipulating to their reliability, the court believes that it is appropriate to note that neither Dr. Vilcek nor anyone else on behalf of Biogen has asserted that the interferon concentrations in the 1,200,000 to 1,600,000 IU/ml range found by Dr. Jones are not substantially different than the product protected by the '779 Patent.

In addition, Berlex notes the testimony of Dr. Susan Goelz of Biogen concerning the production of interferon in "NSO" cells, rather than CHO cells. Mar. 10, 2000 Tr. at 104; Goelz Dep., Brooks Rule 56(f) Decl. Ex. 14, at 517-18. Dr. Goelz was apparently not questioned directly on the issue of equivalents. She did, however, note that "NSO" cells produced interferon "within an order of magnitude of what we see in CHO cells," and agreed that "an order of magnitude" was "ten times." Goelz Dep., Brooks Rule 56(f) Decl. Ex. 14, at 518. Dr. Goelz did not address the implications of this answer for the issue of equivalents. Id. More specifically, she rendered no opinion on whether Biogen's product was substantially different than the composition protected by the '779 Patent and, therefore, gave no reasons for any such opinion.

Thus, the testimony on which Berlex relies in its effort to establish a genuine dispute concerning whether Biogen's product is substantially different than the composition protected by the '779 Patent is flimsier than the evidence deemed to be inadequate in Cypress Semiconductor, 90 F.3d at 1567-68. Berlex, therefore, has not provided the "particularlized testimony" necessary to defeat Biogen's motion for summary judgment on the contention that Biogen infringes the '779 Patent under the doctrine of equivalents. This provides a second reason for granting Biogen's motion for summary judgment on this issue.

VIII. CONCLUSION AND ORDER

For the foregoing reasons, Biogen is entitled to summary judgment on its claims that it does not infringe either the '567 Patent or the '779 Patent literally or under the doctrine of equivalents. The court understands that its construction of the claims in the '567 Patent renders moot Biogen's motion for summary judgment on the question whether the '567 Patent is invalid because it lacks an adequate written specification. The court also understands that in view of its decision that Biogen does not infringe Berlex's patents it is not necessary to decide Biogen's motions for summary judgment concerning alleged inequitable conduct in the prosecutions that resulted in the issuance of the '567 Patent and the '779 Patent. Therefore, the court has not done so.

The court believes that it is now appropriate to enter final judgment for Biogen in an appropriate form.

However, the court wishes: to provide the parties an opportunity to confer; to inform the court of their respective positions on this issue; and, in view of the complex procedural posture of this case created by the many pending motions for summary judgment, furnish the court with a proposed form of judgment.

Accordingly, it is hereby ORDERED that the parties shall, by September 8, 2000 confer, and submit to the court, jointly if possible:

1. A statement concerning whether final judgment for Biogen should now be entered pursuant to Fed.R.Civ.P. 54; and, if so

2. A proposed form of judgment.

EXHIBIT A

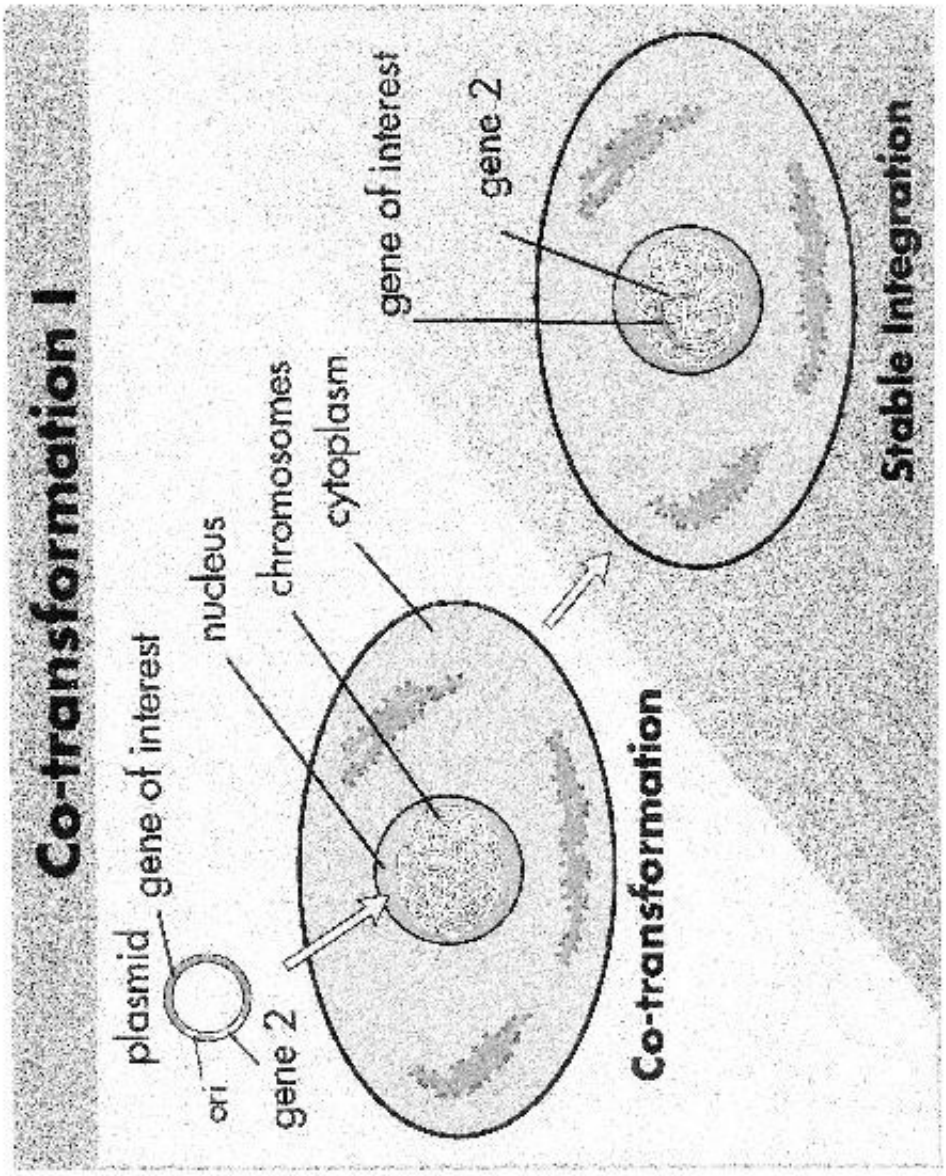

Co-transformation I
plasmid
gene of interest
ori
gene 2
nucleus
chromosomes
cytoplasm
Co-transformation
gene of interest
gene 2
Stable Integration

EXHIBIT B

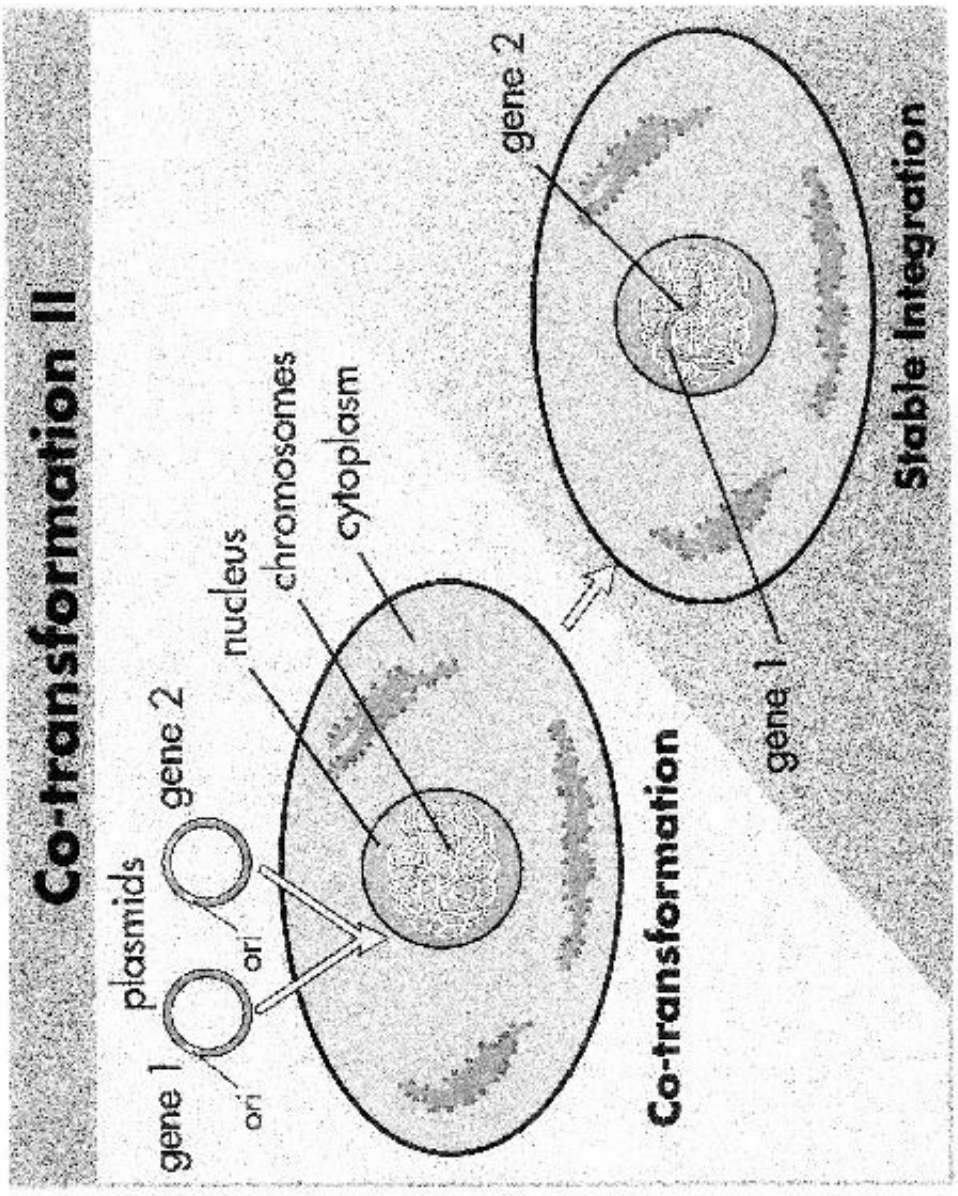

Co-transformation II
plasmids
gene 1
ori
ori
gene 2
nucleus
chromosomes
cytoplasm
Co-transformation
gene 2
gene 1
Stable Integration

EXHIBIT C

TABLE I

EXPRESSION LEVELS OF HUMAN INTERFERON IN CHINESE HAMSTER OVARY CELLS

CHO CELL LINE	IFN	PRO-MOTER	CONSTI-TUTIVE	IFN (U/ml)[1] SUPER INDUCTION[3]	NDV[4]
M12.2	α36	own	10	100	300
PM7	α61	SV40	1000	1000	not done
GC10	β1	SV40	100	100	100
M7.1	β_1	own	100	10,000	1000
M7.1.R10[2]	β_1	own	1000	30,000	—
M7.1.R10 (roller bottle)	β_1	own	10,000	600,000	—

[1]IFN(U/ml) relative to NIH α or β standards on human GM2504 cells with VSV challenge.
[2]M7.1.R10 is a subclone of M7.1 resistant to 10 nM methotrexate.
[3]Superinduction: cells were aged 2 days post confluence, then incubated in fresh medium containing 20 μg/ml poly(I) · poly(C) and 2 μg/ml cycloheximide for 3 hrs. at 37° C.; actinomycin D was then added (2 μg/ml) and cells were incubated 1 hr. at 37° C.; monolayers were washed 3x and fresh medium was replenished; cells were incubated at 37° C and supernatants harvested 24 hrs. later.
[4]NDV induction: cells were grown to confluency, then incubated in fresh medium containing ¼ volume NDV Manhattan strain (titer-5.5 x 10^6) for 24 hrs. at 37° C.; supernatants were harvested, pH was adjusted to 2.0 and supernatant was placed at 0° C. for 4 days; pH was readjusted to 7.0 prior to assay.

SUPPLEMENTAL MEMORANDUM AND ORDER

The court has considered the issues presented by the parties' September 8, 2000 joint submission in response to the August 15, 2000 Memorandum and Order. They are addressed as follows.

1. In the August 15, 2000 Memorandum and Order, at 64-82, the court held that Biogen, Inc. ("Biogen") does not infringe the construct claims in Berlex Laboratories, Inc.'s ("Berlex") U.S. Patent 5,376,567 (the " '567 Patent") under the doctrine of equivalents. The court also found that each of Berlex's method and cell claims involves a single DNA construct which includes an interferon gene and a DHFR gene. Aug. 15, 2000 Mem. and Order at 63. The court's analysis concerning Berlex's contention that Biogen violates the construct claims of the '567 Patent under the doctrine of equivalents is equally applicable to its cell and method claims. Accordingly, Biogen's motion for summary judgment on the issue of equivalents concerning the cell and method claims in the '567 Patent is hereby ALLOWED.

[26] 2. The court has decided that its adoption of Biogen's construction of the claims of the '567 patent renders moot Biogen's motion for summary judgment on the question whether the '567 Patent would be invalid for lack of an adequate written description if Berlex's proposed construction of those claims had

been adopted. Aug. 15, 2000 Mem. and Order at 107. Biogen requests that the court now decide that motion. Berlex contends that it would not be appropriate to do so. The court finds Berlex's position to be persuasive on this question.

The court has for several reasons exercised its discretion to deem Biogen's motion for summary judgment concerning invalidity moot. First, the motion is based on a construction of the claims of the '567 Patent that the court has, as Biogen requested, found to be incorrect. Thus, the motion invites the court to decide a hypothetical question where there may be no genuine case or controversy. Second, if the Court of Appeals for the Federal Circuit disagrees with this court's claim construction it may adopt a claim construction different from that advocated by either party. In any event, if this court's claim construction is found to be incorrect, the guidance of the Court of Appeals for the Federal Circuit will be valuable to this court.

Therefore, Biogen's request that the court now decide its motion for summary judgment on the ground that the '567 patent would be invalid if, contrary to what the court has concluded, Berlex's claim construction were correct is hereby DENIED.

3. The seven minor corrections to the August 15, 2000 Memorandum and Order jointly proposed by the parties are hereby ACCEPTED. A copy of the corrected August 15, 2000 Memorandum and Order is attached hereto as Exhibit 1. [Editor's Note: The corrected memorandum precedes this order in print.]

4. Berlex's proposed form of Final Judgment, attached hereto as Exhibit 2, is hereby ADOPTED and ENTERED.

FINAL JUDGMENT

For the reasons set forth in the Court's August 15, 2000 Memorandum and Order, as supplemented by the Court's September 19, 2000 Supplemental Memorandum and Order, final judgment under Fed.R.Civ.P. 54 is hereby entered in favor of Biogen, Inc. ("Biogen") and against Berlex Laboratories, Inc. ("Berlex") on Berlex's infringement claims regarding U.S. Patents 5,376,567 and 5,795,779.

Biogen's defenses, claims and counterclaims alleging invalidity and unenforceability of the two patents-in-suit are dismissed as moot.

Berlex's motion for Summary Judgment on Biogen's inequitable conduct allegations and Biogen's motion for summary judgment of invalidity under the written description doctrine are dismissed as moot.

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