United States District Court,
D. Delaware.

GLAXO WELLCOME, INC,
Plaintiff.
v.
GENENTECH, INC,
Defendant.

CIV. A. No. 99-335-RRM

April 18, 2001.

In suit alleging infringement of patents for cancer drugs, the District Court, McKelvie, J., held that: (1) phrase "copper ions in an amount sufficient to degrade" required enough copper ions to degrade IgG1 immunoglobulin; (2) phrases "therapeutically effective" and "effective in treating" described treatment with CHO-glycosylated antibodies; (3) term "CDR-grafted" described a recombinant antibody where all six CDRs have been replaced with complete non-human CDRs; and (4) phrases "whole glycosylated recombinant human, chimeric or CDR-grafted or bispecific antibody" and "whole glycosylated recombinant human, chimeric, CDR- grafted or bispecific antibody" required a whole recombinant human, chimeric, CDR-grafted or bispecific antibody that was glycosylated.

Order in accordance with opinion.

Phrases "whole glycosylated recombinant human chimeric or CDR grafted or bispecific antibody" and "whole glycosylated recombinant human, chimeric, CDR-grafted or bispecific antibody" in patents claiming an improvement in a method for treating human diseases, disorders, or cancer with whole glycosylated recombinant human chimeric, CDR-grafted, or bispecific antibodies glycosylated by a Chinese hamster ovary (CHO) cell described a whole recombinant human, chimeric, CDR-grafted, or bispecific antibody that was glycosylated.

James M. Mulligan, Jr., Connolly Bove Lodge & Hutz, LLP, Wilmington, DE, Stephen B. Judlowe, Brian P. Murphy, Robert G. Gibbons, Jason A. Lief, Richard J. McCormick, Jeffrey M. Gold, Christine A. Pepe, Hopgood, Calimafde, Kalil & Judlowe, LLP, New York City, plaintiff.

Philip A. Rovner, Potter Anderson & Corroon LLP, Wilmington, DE, Leora Ben-Ami, Jason E. Kidd, Patricia A. Carson, Vladimir V. Drozdoff, Clifford Chance Rogers & Wells LLP, New York City, for defendant.

REVISED OPINION

McKELVIE**, District Judge.**

This is a patent case. Plaintiff Glaxo Wellcome Inc. ("Glaxo") is a North Carolina corporation with its principal place of business in Research Triangle Park, North Carolina. Glaxo is a subsidiary of Glaxo Wellcome plc, a company based in the United Kingdom. Glaxo owns U.S. Patent Nos. 5,654,403 and 5,792,838 (collectively, the "Smith patents") and U.S. Patent Nos. 5,545,403 and 5,545,405 (collectively, the "Page patents"). Defendant Genentech, Inc. is a Delaware corporation with its principal place of business in San Francisco, California.

The parties dispute whether Herceptin and Rituxan, two cancer drugs developed by Genentech, infringe one or more claims of the Smith and Page patents. Genentech sells Herceptin and Rituxan throughout the United States. The Food and Drug Administration has approved Rituxan for the treatment of patients with relapsed or refractory low-grade or follicular, CD-20 positive, B-cell non-Hodgkins lymphoma. Herceptin is currently undergoing clinical studies and can be administered to patients with metastic breast cancer whose tumors overexpress the HER2 protein.

The Smith patents claim a stabilized immunoglobulin composition containing copper ions with an amount of a chelator of copper ions sufficient to bind the copper ions present in the composition, and the method for creating the composition. The Page patents claim an improvement in a method for treating human diseases, disorders or cancer with whole glycosylated recombinant human chimeric, CDR-grafted or bispecific antibodies glycosylated by a Chinese hamster ovary cell.

On May 28, 1999, Glaxo filed a complaint alleging that Genentech infringes one or more claims of the Smith and Page patents. Genentech answered the complaint on July 19, 1999, denying Glaxo's allegation of infringement, asserting affirmative defenses of invalidity and unenforceability, and seeking a declaratory judgment of noninfringement, invalidity and unenforceability. On March 16, 2000, the court granted Genentech's motion to amend its pleading to assert additional counterclaims for invalidity and unenforceability of the Smith patents. On March 31, 2000, Genentech moved for a partial summary judgment that it does not infringe the claims of the Smith patents. On July 28, 2000, the court found that there were genuine issues of material fact as to the scope of the Smith patent claims and denied Genentech's motion for summary judgment.

On October 27, 2000, Glaxo moved for partial summary judgment that Genentech infringes the claims of the Page patents. In response, Genentech moved for cross-partial summary judgment that it does not infringe the Page patents. Between February 7, 2001 and March 9, 2001, Genentech moved for summary judgment based on various affirmative defenses.

On March 2, 2001, the parties submitted proposed claim constructions of the Smith and Page patents. This is the court's construction of the Smith and Page claims.

I. *FACTUAL AND PROCEDURAL BACKGROUND*

The court draws the following facts from the affidavits and documents submitted by the parties and from prosecution histories of the patents at issue.

A. *General Description of the Technology*

The patents at issue relate to technology for stabilizing antibodies against degradation and preventing human rejection of antibodies derived from non-human cells. Antibodies or immunoglobulins are proteins made by

the human body's immune cells to defend against disease. The body makes specific antibodies in response to different disease-causing agents called antigens. The body produces specialized antibodies to defend against particular antigens. The antibodies bind to their complementary antigens and initiate immune attacks that destroy the antigens.

Antibodies have a shape that is typically depicted graphically as a "Y." Four protein chains combine to create a single antibody. Two long chains called "heavy chains" correspond to the entire length of the "Y," while two shorter chains called "light chains" correspond to the arms of the "Y." The tips of the "Y," called complementarity-determining regions ("CDRs"), are responsible for binding to the antigen.

Humans and other living organisms store information needed to produce proteins such as antibodies in their molecules of deoxyribonucleic acid ("DNA"). Using genetic engineering and recombinant DNA technology, scientists are able to create identical copies of specific antibodies that react with particular antigens. Antibodies created this way are referred to as "monoclonal antibodies."

Scientists identify the strands of DNA containing the code for particular antibodies and introduce these DNA strands into living cells called "host cells." Commonly used host cells include bacterial or mammalian cells which can be reproduced in the laboratory. The host cells are reproduced in a nutrient medium which generally contains an energy source and the vitamins and minerals needed to support the cells' metabolic process. Metal ions are often added to the cell culture medium because metal ions improve the growth of the host cells.

As the host cells containing the artificially-introduced DNA grow and replicate in the culture medium, the cells produce the desired antibody along with other proteins normally made by the cells. The desired antibody is then extracted from the host cells and purified through a series of steps which enrich the antibody by selectively removing undesired material. Scientists have found that the metal ions which promote cell growth in the host cells have the detrimental effect of degrading the antibodies when they are removed from the host cells. To improve the stability of monoclonal antibodies, scientists attempt to remove the metal ions during antibody purification. The technology of the Smith patents relates to this process.

In order for foreign antibodies to bind to antigens in humans, scientists must prevent the human immune system from rejecting the foreign antibodies. Glycosylation makes preventing human rejection difficult. Glycosylation is the process by which each bacterial or mammalian species and cell type therein attaches a distinct carbohydrate unit to the antibodies it produces. That is, different host cells will glycosylate antibodies with distinct carbohydrate chains regardless of the antibody DNA blueprint with which they are transfected. Such antibodies may or may not be tolerated by human patients and may or may not provide for therapeutic treatment of disease. To increase the likelihood of human tolerance, scientists attempt to create glycosylated antibodies that human cells will not reject. The technology of the Page patents relates to this process.

B. ***The Smith Patents***

Marjorie Smith and Valentina Riveros-Roja are two scientists at Glaxo who set out to improve the stability of monoclonal antibodies. Smith and Riveros-Roja discovered a process for stabilizing an immunoglobulin composition containing copper ions by adding a chelator of copper ions. In 1994 and 1995, Smith and Riveros-Roja submitted applications to the U.S. Patent and Trademark Office ("PTO") for two patents based on their invention. In the first application for U.S. Patent No. 5,654,403 (the '403-S patent FN1), the

inventors claim a stabilized immunoglobulin composition containing copper ions and an amount of a chelator of copper ions sufficient to bind the copper ions present in the composition. In the second application for U.S. Patent No. 5,792,838 (the '838 patent), the inventors claim the method for stabilizing an immunoglobulin composition containing copper ions by adding a chelator of copper ions.

FN1. The addition of "-S" distinguishes the Smith '403 patent from the Page '403 patent.

1. *Prosecution History of the '403-S Patent*

a. *Application of April 28, 1994*

On April 28, 1994, inventors Smith and Riveros-Rojas applied for a patent for a stabilized immunoglobulin composition containing copper ions and a chelator of copper ions. As it was originally submitted, the application for the '403-S patent contains 21 claims. The application includes claims for the process that were later withdrawn and re-submitted in a separate application for the '838 patent.

In the patent specification, the applicants explain that their invention is based on the "surprising discovery that trace amounts of copper ($Cu^{//}$) have a destabilizing effect on immunoglobulin molecules on storage and that this effect can be eliminated by formulating the immunoglobulin with a suitable chelator of copper ions." The specification further provides:

It has also surprisingly been found that a presence of a chelator of copper ions may have a stabilizing effect on the immunoglobulin molecule even when the immunoglobulin does not contain amounts of copper which are detectable by conventional techniques such as atomic absorption spectroscopy. Whilst not wishing to be bound by any particular theory, it may be that the presence of copper ions in amounts below the detectable limits of techniques such as atomic absorption spectroscopy still has a destabilizing effect on the immunoglobulin molecule which can be eliminated by the addition of a suitable chelating agent.

According to the applicants, a "stabilizing amount of a chelator of copper ions such as EDTA or citrate" is added to the immunoglobulin to ensure that any copper present is bound by the chelating agent and thus rendered ineffective in destabilizing the immunoglobulin. The specification further provides that a "particularly preferred metal ion chelating agent" is ethylenediamine tetraacetic acid ("EDTA").

In the original application, Claim 1 reads as follows:

1. A stabilized immunoglobulin composition comprising at least one immunoglobulin together with a stabilizing amount of a chelator of copper ions.

b. *Office Action of October 5, 1994*

On October 5, 1994, the examiner issued a restriction requirement because the claims were directed to more than one invention. According to the examiner, Claims 1-15 were drawn to a stabilized immunoglobulin composition, while Claims 16-21 were drawn to a process for enhancing the stability of an immunoglobulin. The examiner stated that the stabilized immunoglobulin composition in the first invention would not suggest the stabilizing process in the second invention. Therefore, the examiner directed the applicants to elect a single invention.

The examiner further stated that regardless of which invention the applicants elected to pursue, they were required under 35 U.S.C. s. 121 to elect a single disclosed species to which their claims would be restricted if no generic claim was finally held allowable.FN2 According to the examiner, if the applicants pursued Claims 1-15, they were required to elect a specific antibody stabilized by a specific chelator of copper ions. If the applicants pursued Claims 16-21, they were required to elect a specific purified immunoglobulin.

FN2. 35 U.S.C. s. 121 provides in pertinent part:
If two or more independent and distinct inventions are claimed in one application, the Director may require the application to be restricted to one of the inventions.

c. *Response of November 8, 1994*

On November 8, 1994, the applicants submitted a response to the PTO's restriction requirement. The applicants elected to prosecute Claims 1-15 and they elected anti-CD4 as the specific antibody for those claims.

d. *Rejection of January 26, 1995*

On January 26, 1995, the examiner rejected Claims 1-15 and withdrew Claims 16-21 from further consideration. The examiner stated that the claimed "chelator of copper ions" was not properly enabled under 35 U.S.C. s. 112.FN3 According to the examiner, "[b]esides EDTA and sodium citrate, the specification does not provide any guidance as to what other chelator of copper ions can be used to stabilize an immunoglobulin...." The examiner also objected to the claimed "chelator of copper ions" under 35 U.S.C. s. 112, as indefinite and ambiguous.FN4

FN3. 35 U.S.C. s. 112 provides:
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.

FN4. 35 U.S.C. s. 112 provides:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The examiner further rejected the claims as obvious under 35 U.S.C. s. 103 in light of a number of prior art references including U.S. Patent No. 5,367,060 (the '060 patent).FN5 The '060 patent issued to Genentech as assignee of inventors Richard L. Vandlen and William E. Holmes on November 22, 1994. According to the examiner, the '060 patent teaches that therapeutic formulations of antibodies can be prepared for storage by mixing the antibodies with stabilizers such as EDTA or citrate in the form of lyophilized cake or aqueous solutions. Therefore, the examiner wrote that "it would have been obvious to one of ordinary skill in the art at the time the [Glaxo] invention was made to mix the chelator of copper ions with the antibody with the

expectation that the copper ions attached to the antibody would be removed by the chelator and that the antibody would be stabilized."

FN5. 35 U.S.C. s. 103(a) provides:
A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains.

e. *Amendment of April 26, 1995*

On April 26, 1995, the applicants submitted an amendment to the PTO. The applicants canceled Claims 1-21 from the original application and substituted 17 new claims numbered 22-38. In Claim 22, which later issued as Claim 1 of the '403-S patent, the applicants claim a composition comprising immunoglobulin and an amount of a chelator of copper ions sufficient to bind to copper ions present in the composition. Claim 22 reads as follows:

22. A stabilized immunoglobulin composition comprising an IgG_1 immunoglobulin together with an amount of a chelator of copper ions sufficient to bind copper ions present in the solution and protect the immunoglobulin from degradation by the copper ions.

In response to the examiner's objection that the claimed "chelator of copper ions" was not enabled, the applicants stated that no objective evidence was presented to show that it would require more than routine experimentation for one of ordinary skill in the art to determine which chelators are best suited for use in the invention. The applicants argued that "chelator of copper ions" was enabled because the specification provides examples of embodiments within the class.

The applicants also disagreed with the examiner's decision that the claimed "chelator of copper ions" was indefinite and ambiguous. According to the applicants, "[c]opper chelators have been known in the prior art for many years and one of ordinary skill in the art would have no difficulty selecting a compound to add to an antibody composition to chelate copper ions present in the composition."

In response to the examiner's rejection of the claims for obviousness in light of the '060 patent and other prior art references, the applicants suggested that their invention was distinguishable from the prior art in part based on the presence of copper ions in the immunoglobulin composition. The applicants wrote:

There is no suggestion in the '060 patent that [chelators] be used in compositions of HRG or HRG antibodies to bind copper ions present in the compositions. More specifically, there is no discussion at all in the patent that copper ions may be present in the antibody compositions, that the presence of even minute amounts of copper in an antibody composition can cause the degradation of the antibody during storage or that this degradation can be avoided by adding to such compositions a chelator of copper ions in an amount sufficient to bind the copper ions present in the composition.

According to the applicants, none of the prior art references, taken alone or in combination, suggested that copper ions could degrade immunoglobulins, or that immunoglobulins could be stabilized with a chelator of

copper ions. The applicants stated that "[t]he examiner's statement that the present invention differs from the primary reference 'only' by the use of the chelator of copper ions to stabilize the antibody is hardly a trivial distinction, as this was the very focus of the present invention." Therefore, the applicants argued that the prior art references cited by the examiner did not render their invention obvious under 35 U.S.C. s. 103.

f. ***Final Rejection of July 10, 1995***

On July 10, 1995, the examiner sent the inventors a final action letter canceling Claims 1-21 and rejecting Claims 22-36.FN6 The examiner rejected Claims 22-36 for the same reasons that she had previously rejected the corresponding Claims 1-15.

FN6. The examiner also withdrew Claims 37 and 38. The examiner stated that the Claims 37 and 38 were distinct from the invention because the claims were equivalent to cancelled, non-elected Claims 18 and 19.

The examiner maintained her objection to the claimed "chelator of copper ions" in Claims 22 and 28 (previously Claims 1 and 11), for lack of enablement. After considering the applicants' arguments, the examiner wrote, "the fact remains that only EDTA and citrate ion are disclosed in the specification as the chelator of copper ions." According to the examiner, it would take undue experimentation to determine which chelators of copper ions could be used in the invention. The examiner also maintained the objection to "chelator of copper ions" as indefinite under 35 U.S.C. s. 112.

Furthermore, the examiner rejected Claims 22-36 as obvious in light of the '060 patent and other prior art references. The examiner stated that the '060 patent teaches that a therapeutic formulation of HRG antibody can be prepared for storage by mixing the antibody with stabilizers such as EDTA and citrate. Among the stabilizers listed in the '060 patent, the examiner stated that only citrate and EDTA are chelating agents. The examiner wrote, "[s]ince citrate and EDTA are chelating agents, it is obvious to one skilled in this art to use said chelating agents as stabilizers to remove any metals that are bound by said chelating agents including copper ions present in the immunoglobulin composition."

g. ***Interview Summary Record of November 9, 1995***

On November 9, 1995, the examiner issued an Interview Summary Record from her interview with the applicants on that day. The Interview Summary Record states: "We agreed that the s. 112, para. 1 enablement & scope will be withdrawn. We agreed that an amendment regarding the level of copper and stabilizer in the solution would probably overcome the s. 103 objections."

h. ***Response of January 11, 1996***

On January 11, 1996, the applicants submitted an amendment to the PTO. The applicants amended Claim 22 "to make explicit that which was implicit in the claim before, namely, that the composition of IgG_1 immunoglobulin also contains copper ions." Claim 22, as submitted in the proposed amendment, reads as follows, with the underlining and brackets indicating added and retracted language, respectively:

22. *In an* [A stabilized] immunoglobulin composition *of* [comprising] IgG_1 immunoglobulin *containing copper ions in an amount sufficient to degrade the immunoglobulin, wherein the improvement comprises the addition of* [together with] an amount of a chelator of copper ions sufficient to bind *the* copper ions present

in the [solution] *composition* and protect the immunoglobulin from degradation by the copper ions *and thus stabilize the IgG_1 composition*.

The applicants also added a new Claim 39, which later issued as Claim 16 of the '403 patent. As it was submitted in the amendment, Claim 39 reads as follows:

39. A stabilized immunoglobulin composition comprising an IgG_1 immunoglobulin and copper ions, wherein the copper is present in an amount sufficient to degrade the immunoglobulin, together with an amount of chelator of copper ions sufficient to bind the copper ions present in the composition and protect the immunoglobulin from degradation by the copper ions.

The applicants stated that the claimed composition had sufficient amounts of chelator to bind "trace amounts of copper" to prevent the degradation of the immunoglobulin that the copper would otherwise cause. According to the applicants, such compositions are not rendered obvious by the teachings of the '060 patent or the other prior art references cited by the examiner.

i. *Notice of Allowability*

On March 19, 1996, the examiner allowed Claims 22-36 and Claim 39 of the application as amended. The claims were re-numbered 1-16.

j. *Issuance of the '403-S Patent*

On August 5, 1997, the PTO issued the '403-S patent to Glaxo as assignee of the inventors, Marjorie Smith and Valentina Riveros-Roja.FN7 The '403-S patent is entitled "Immunoglobulins Stabilized with a Chelator of Copper Ions."

FN7. The '403 patent lists Burroughs Wellcome Co. as assignee. Burroughs Wellcome merged with Glaxo Inc. in 1995 to form Glaxo Wellcome Inc.

2. ***Prosecution History of*** the '838 Patent

a. *Application of June 5, 1995*

On June 5, 1995, Smith and Riveros-Rojas applied for a patent for a method for stabilizing an immunoglobulin composition containing copper ions by adding a chelator of copper ions. As noted above, certain claims of this application were included together with the composition claims in the application for the '403-S patent. As a result, the original application for the '838 patent is virtually identical to the application for the '403-S patent. Because the application for the '838 patent is a continuation of the application for the '403-S patent, the patents share a common specification.

In the original application, Claim 11 reads as follows:

11. Use of a chelator of copper ions to stabilize an immunoglobulin against degradation on storage.

b. *Preliminary Amendment of July 22, 1995*

On July 22, 1995, the applicants submitted a preliminary amendment to the PTO. The applicants modified several claims in the original application to change them from a "use" claim format to a "method" claim format. For example, Claim 11 was amended as follows, with the underlining and brackets indicating added and retracted language, respectively:

11. (amended) [Use of a chelator of copper ions to stabilize] *A method for stabilizing* an immunoglobulin against degradation on storage *which comprises adding to said immunoglobulin a chelator of copper ions in an amount sufficient to stabilize said immunoglobulin*.

c. *Preliminary Amendment of June 20, 1996*

On June 20, 1996, before the examiner considered the application for the '838 patent, the applicants filed a second preliminary amendment. The applicants canceled Claims 1-10 and amended Claim 11 to state that the immunoglobulin composition contains "copper ions in an amount sufficient to degrade the immunoglobulin." Claim 11, as amended, reads as follows, with the underlining and brackets indicating added and retracted language, respectively:

11. (twice amended) A method for stabilizing *against degradation on storage* an immunoglobulin *composition of IgG_1 which contains copper ions in an amount sufficient to degrade the immunoglobulin* [against degradation on storage] which comprises adding to said immunoglobulin a chelator of copper ions in an amount sufficient to stabilize said immunoglobulin.

d. *Office Action of October 2, 1996*

On October 2, 1996, the examiner canceled Claims 1-10 and issued a restriction requirement for Claims 11-21. According to the examiner, Claims 11-21 were directed to more than one invention. Claims 11-15 and 18-21 were drawn to a method of stabilizing immunoglobulin solutions against copper ion degradation and a composition of immunoglobulins substantially free of copper ions. Claims 16-17 were drawn to a second method for stabilizing a immunoglobulin. The examiner directed the applicants to elect a single invention.

e. *Response of December 2, 1996*

On December 2, 1996, the applicants submitted a response to the examiner's restriction requirement. The applicants elected to pursue Claims 11-15 and 18-21, and stated that the non-elected matter would be deleted.

f. *Preliminary Amendment of April 9, 1997*

On April 9, 1997, the applicants submitted a fourth preliminary amendment to the PTO. The applicants canceled Claim 11 and added a new Claim 24. In the amendment, Claim 24, which later issued as Claim 1 of the '838 patent, reads as follows:

24. A method of making a stabilized IgG_1 composition comprising adding to a starting composition comprising:

i) IgG_1 and

ii) copper ions in an amount sufficient to degrade said IgG_1, an amount of a chelator of copper ions sufficient to stabilize said IgG_1 against copper ion-mediated degradation, so that said stabilization IgG_1 composition is made.

g. *Interview Summary of May 27, 1997*

On May 27, 1997, the examiner issued a Interview Summary of his May 21, 1997 interview with the applicants. The InterviewSummary states: "Applicant consults regarding claim language. Examiner indicated a statement would be made in reasons for allowance regarding starting composition. Applicant agreed with proposed statement regarding starting composition."

h. *Notice of Allowability*

On May 27, 1997, the examiner allowed Claims 24 and 12-15 of the application, as amended. The claims were re-numbered 1-5. In a statement of reasons for allowance, the examiner stated that "the method claims of this application are allowable given the allowance of the ['403 patent] claiming the compounds. The starting composition of Claim 1 is considered to comprise IgG_1 class antibodies and an amount of copper sufficient to degrade the IgG_1 antibodies."

i. *Issuance of* the '838 Patent

On August 11, 1998, the PTO issued the '838 patent to Glaxo as assignee of the inventors Smith and Riveros-Rojas. The '838 patent is entitled "Method for Stabilizing Immunoglobulin Compositions."

C. *The Page Patents*

Martin J. Page and J. Scott Crowe are two scientists at Glaxo who decided to improve the therapeutic effects of non-human glycosylated antibodies in humans. Page and Crowe claim to have discovered that in a proper, defined manner, antibodies raised and glycosylated in Chinese hamster ovary ("CHO") cells can be tolerated by the human immune system and serve as a therapeutically effective medicine. In 1993, Page and Crowe submitted applications to the PTO for two patents based on their discovery. In the first application for U.S. Patent No. 5,545,403 (the '403-P patent FN8), the inventors claim an improvement in a method for treating human diseases or disorders with whole glycosylated recombinant human chimeric, CDR-grafted or bispecific antibodies glycosylated by a Chinese hamster ovary cell. In the second application for U.S. Patent No. 5,545,405 (the '405 patent), the inventors claim the same improvement with regard to cancer rather than human diseases and disorders. The patents share a common specification.

FN8. The addition of "-P" distinguishes the Page '403 patent from the Smith '403 patent.

1. *Prosecution History of the '403-P Patent*

a. *Application of November 23, 1993*

On November 23, 1993, inventors Page and Crowe applied for a patent for a method of treating human diseases and disorders by administering a CHO-glycosylated cell. As it was originally submitted, the application for the '403-P patent contains 26 claims.

In the original patent specification, the applicants observed that prior to their invention, the process of creating antibodies through myeloma cells, a natural host specialized for antibody production and secretion, required complex vector design and resulted in highly variable expression levels. The applicants further observed that "[a]n alternative mammalian expression system is that offered by the use of ... Chinese hamster ovary (CHO) cells." Based on this system, the applicants explained as follows:

A process has now been developed that enables balanced expression of the light and heavy chains of an antibody from CHO cells. Balanced expression is desirable given that the light and heavy chains are linked together in the antibody molecule in equimolar proportions. This process allows the antibody to be obtained in functional form and to be secreted in good yields. Thus, the process enables sufficient quantities of functionalantibody to be obtained for use in the immunotherapy of pathological disorders.

According to the application, the inventions were: (1) the cell line capable of producing "all kinds of antibodies that generally comprise equimolar proportions of light and heavy chains" (Claims 1-13); (2) the antibodies created by the cell line (Claims 14-16); (3) the process for the preparation of an antibodies derived from the cell line (Claim 17); (4) methods for treating various human disorders, "which comprise[ ] administering a therapeutically effective amount[s] of an antibody" developed from the cell line (Claims 18-25); and (5) a formulation "comprising a combination of a CHO-glycosylated antibody ... and a physiologically acceptable diluent or carrier" (Claim 26).

b. *Preliminary Amendment of November 23, 1993*

On November 23, 1993, counsel for the applicants filed a Preliminary Amendment with the PTO. In the amendment, the applicants cancelled Claims 1-18, added Claims 27-37 and amended Claims 19-22.

Claim 19 originally claimed "[a] method for treating severe vasculitis, systemic lupus, multiple sclerosis, graft vs. host disease, psoriasis, juvenile onset diabetes, thyroid disease, myasthenia gravis, transplant rejection or asthma which comprises administering a therapeutically effective amount of an antibody of claim 14, 15 or 16." In the applicants' amended Claim 19, "an antibody of claim 14, 15 or 16" was replaced with "a human or altered antibody having CHO-glycosylation." The applicants made the same modification to Claims 20-22.

Claims 27 and 28 focused on a method for treating various diseases and disorders, including T-cell mediated disorders, such as vasculitis and systemic lupus; autoimmune disorders, such as multiple sclerosis and Sjogrens' disease; cancers such as non-Hodgkin lymphoma; and infectious diseases like herpes. Claims 29-31 were directed to a method of suppressing a patient's immune response through the administration of an immunosuppressive human or altered antibody having CHO glycosylation. Claim 32 focused on a method of treating a disease which can be treated through the administering of a therapeutic human or altered antibody having CHO glycosylation. Claim 33 was directed to a method of providing immunotherapy by administering a therapeutic CHO-glycosylated human or altered antibody which could initiate the effector function of the antibody. Claim 34 focuses on a method for treating a disorder through the suppression of the patient's immune system which comprises administering an immunosuppressive human or altered antibody having CHO glycosylation. Claims 35-37 were directed to a method of treating T-cell mediated disorder by administering a CHO-glycosylated human or altered therapeutic antibody which recognizes an antigen binding site on a T-cell marker.

c. *Preliminary Amendment of March 30, 1994*

On November 30, 1994, counsel for the applicants filed a second Preliminary Amendment with the PTO explaining that the '403-P patent application was a continuation application of application Serial Number 08/046,893. The PTO had issued an Office Action with regard to the parent application rejecting certain claims. In the Preliminary Amendment, the applicants disputed the PTO's rejection of the parent application claims to the extent that they were the same claims set forth in the '403-P application.

d. ***Office Action of August 5, 1994***

On August 5, 1994, the examiner noted that the application contained a number of claims directed to patentably distinct species of the claimed invention, and explained that these species differed with respect to their etiologies. The examiner further explained that "[a] method for treating one disease is not obvious in view of another." To remedy the problem, the examiner instructed the applicants to elect a single species for prosecution in the event that no generic claim was deemed allowable.

e. ***Amendment of September 15, 1994***

On September 15, 1994, the applicants cancelled claims 19-37 in response to the Office Action of August 5, 1994. The applicants added Claim 38, which later issued as Claim 1 of the '403-P patent. Claim 38 stated as follows:

38. In a method for treating a mammal suffering from a disease or disorder by administering glycosylated human or altered antibody wherein said antibody is effective in treating said disease or disorder in said mammal, the improvement which comprises administering a therapeutically effective amount of a CHO-glycosylated form of said antibody.

Claim 38 was the only claim going forward in the prosecution.

f. ***Office Action of December 9, 1994***

On December 9, 1994, the PTO issued an Office Action rejecting Claim 38. First, the examiner rejected the claim "as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." Specifically, the examiner found that the word "altered" was unclear. Second, the examiner found that Claim 38 was anticipated by Cabilly et al. (U.S. Patent 4,816,567), which teach altered antibodies expressed in CHO cell lines. Third, the examiner found that Claim 38 was anticipated by Bodmer et al. (U.S. Patent 5,219,996), which teach the use of CHO cells to produce chimeric B72.3 antibody. Fourth, the examiner rejected Claim 38 based on the doctrine of obviousness.

g. ***Amendment of February 28, 1995***

On February 28 1995, applicants responded to the Office Action of December 9, 1994 by amending Claim 38 as follows, with the underlining and brackets indicating added and retracted language, respectively:

38 (amended). In a method for treating a (mammal) *human* suffering from a disease or disorder [by] *comprising* administering a *therapeutically effective amount of a whole* glycosylated human, [or altered] *chimeric, CDR-grafted or hybrid antibody,* wherein said antibody is effective in treating said disease or disorder in said [mammal] *human,* the improvement [which comprises administering a therapeutically effective amount of a CHO-glycosylated form of said antibody] wherein the Fc region of said antibody has CHO glycosylation.

The applicants also added Claims 39-44, which later issued as Claims 2-7. Claim 39 claimed "[t]he method of claim 38, wherein said antibody is an antibody against CD4." Claim 40 claimed "[t]he method of claim 38, wherein said antibody is an antibody against CDw52." Claim 41 claimed "[t]he method of claim 39, wherein said antibody is a CDR-grafted antibody." Claim 42 claimed "[t]he method of claim 40, wherein said antibody is a CDR-grafted antibody." Claim 43 claimed "[t]he method of claim 39, wherein said antibody is a chimeric antibody." Claim 44 claimed "[t]he method of claim 40, wherein said antibody is a chimeric antibody."

i. ***Notice of Allowability***

On June 13, 1995, the PTO issued a Notice of Allowability with an Examiner's Amendment to the claims. The examiner amended Claim 38 as follows, with the underlining and brackets indicating added and retracted language, respectively:

Claim 38 (twice amended). In a method for treating a [mammal] human suffering for a disease or disorder [by] comprising administering a therapeutically effective amount of a whole glycosylated *recombinant* human [or altered] chimeric or CDR-grafted or [hybrid] *bispecific* antibody [wherein said antibody is] effective in treating said disease or disorder in said human, *wherein* the improvement [which comprises administering a therapeutically effective amount of a CHO-glycosylated form of said antibody wherein the Fc region of said antibody has CHO glycosylation] *comprises an antibody glycosylated by a Chinese hamster ovary cell*.

The examiner also amended Claims 39 and 40. Claim 39 (amended) claimed "[t]he method of claim 38, wherein said antibody [is an antibody against] *specifically binds* CD4." Claim 40 (amended) claimed "[t]he method of claim 38, wherein said antibody [is an antibody against] *specifically binds* CDw52." The examiner renumbered Claims 38-44 as Claims 1-7.

j. ***Issuance of the '403-P Patent***

On August 13, 1996, the PTO issued the '403-P patent to Glaxo as assignee of the inventors Page and Crowe. The '403-P patent is entitled "Method for Treating a Mammal by Administering a CHO-Glycosylated Antibody."

2. ***Prosecution History of*** the '405 Patent

a. ***Application of November 3, 1994***

On November 3, 1994, Page and Crowe applied for a patent claiming: (1) the CHO cell line that produces the glycosylated antibodies (Claims 1-13); (2) human or altered antibodies having been glycosylated in CHO cells (Claims 14-16); (3) methods for creating medicaments that comprise CHO-glycosylated antibodies (Claims 17-18); (4) a method of treating a number of specific human diseases, including cancer, by administering CHO-glycosylated antibodies (Claims 19-25); and (4) a formulation comprising a CHO-glycosylated antibody and an acceptable dilutant (Claim 26). As it was originally submitted, the application for the '405 patent contains 26 claims. The bases for their invention are substantially similar to those set forth in original specification of the '403-P patent.

b. ***Preliminary Amendment of November 3, 1994***

On November 3, 1994, the applicants filed a preliminary amendment with the PTO. In the amendment, the applicants added Claims 38-47, which would later become Claims 27-36. Claim 38 claimed as follows:

Claim 38. In a method for treating a mammal suffering from cancer by administering a human or altered antibody wherein said antibody is effective in treating said cancer, the improvement which comprises administering a therapeutically effective amount of a CHO-glycosylated form of said antibody.

Claims 39 applies the method to the treatment of non-Hodgkins lymphoma, and Claim 40 applies it to multiple myeloma. Claim 41 claims the method where the glycosylated antibody is chimeric or CDR-grafted. Claim 42 claims the method where the antibody specifically recognizes a T-cell marker. Claim 43 claims the method where the antibody is an anti-CDw52 antibody. Claim 44 claims the method where the antibody is a cancer cell marker antigen. Claim 45 claims the method where the antibody is an anti-CD33 antibody or an anti-CD38 antibody. Claims 46 and 47 claim the method with a recommended dosage and treatment period.

c. *Office Action of January 11, 1995*

On January 11, 1995, the examiner rejected Claims 1 and 27-36 pursuant to 35 U.S.C. s. 101 because they claimed the same invention as a co-pending application. The examiner also rejected Claims 27-36 because the invention was inoperable and lacked patentable utility. The examiner rejected the specification for "failing to provide an adequate written description of the invention and for failing to adequately teach how to make and/or use the invention, i.e. for failing to provide an enabling disclosure," and further rejected Claims 27-36 on the same grounds.

The examiner rejected Claims 1, 27-31 and 33 pursuant to 35 U.S.C. s. 102(b) as being anticipated by Bodmer et al., which teach the use of CHO cells to produce chimeric B72.3. Bodmer et al. further teach that the antibodies can be used in the treatment of cancers, including non-Hodgkins lymphoma and multiple myeloma The examiner also rejected Claim 1 because it was anticipated by Cabilly et al., which teach altered antibodies expressed in CHO cell lines.

The examiner rejected Claims 32 and 24-46 pursuant to 35 U.S.C. s. 103 as being unpatentable over Bodmer et al., and further rejected Claims 27-36 as unpatentable over Cabilly et al. The examiner also acknowledged that Claims 27-36 were drafted in Jepson format.

d. *Amendment of May 11, 1995*

On May 11, 1995, the applicants responded to the Office Action of January 11, 1995 by cancelling Claim 1 without prejudice and amending Claim 27 (previously Claim 38) as follows, with the underlining and brackets indicating added and retracted language, respectively:

Claim 27 (amended). In a method for treating a mammal suffering from cancer by administering a *therapeutically effective amount of whole glycosylated* human or altered antibody wherein said antibody is effective in treating said cancer, the improvement [which comprises administering a therapeutically effective amount of a CHO-glycosylated form of said antibody] *wherein the Fc region of said antibody has CHO glycosylation*.

e. *Notice of Allowability*

On June 8, 1995, the PTO issued a Notice of Allowability with an Examiner's Amendment to the claims. The examiner renumbered the claims, and amended Claim 1 (previously Claim 27) as follows, with the underlining and brackets indicating added and retracted language, respectively:

Claim 1 (twice amended). In a method for treating a mammal suffering from cancer by administering a therapeutically effective amount of a whole glycosylated *recombinant* human [or altered] *chimeric or CDR-grafted* antibody [wherein said antibody is] effective in treating said cancer, *wherein* the improvement [wherein the Fc region of said antibody has CHO glycosylation] *comprises an antibody glycosylated by a chinese hamster ovary cell*.

The examiner also canceled what had previously been Claim 30.

f. *Amendment of September 6, 1995*

On September 6, 1995, the applicants amended Claim 1 as follows, with the underlining and brackets indicating added and retracted language, respectively:

Claim 1 (thrice amended). In a method for treating a [mammal] *human* sufferingfrom cancer by administering a therapeutically effective amount of whole glycosylated recombinant human, chimeric, [or] CDR grafted *or bispecific* antibody effective in treating said cancer, wherein the improvement comprises an antibody glycosylated by a Chinese hamster ovary cell.

g. *Issuance of* the '405 Patent

On August 13, 1996, the PTO issued the '405 patent to Glaxo as assignee of the inventors Page and Crowe. The '403-P patent is entitled "Method for Treating a Mammal Suffering From Cancer with a CHO-Glycosylated Antibody."

D. *The Lawsuit*

On May 28, 1999, Glaxo filed a complaint in this court alleging that Genentech's cancer drugs, Herceptin and Rituxan, infringe one or more claims of the Smith and Page patents. Genentech answered the complaint on July 19, 1999, denying Glaxo's allegation of infringement, asserting affirmative defenses of invalidity and unenforceability, and seeking a declaratory judgment of noninfringement, invalidity and unenforceability. On January 31, 2000, Genentech moved to amend its pleading to assert additional counterclaims for invalidity and unenforceability of the Smith patents. On March 16, 2000, the court granted Genentech's motion.

On March 31, 2000, Genentech moved for a partial summary judgment that it does not infringe the claims of the Smith patents. On April 21, 2000, Glaxo submitted its answering brief in opposition to Genentech's motion for summary judgment. Glaxo argued that Herceptin and Rituxan infringe the Smith patents because both accused products contain all of the claim limitations of the patents. Glaxo also argued that summary judgment was not appropriate because there were genuine issues of material fact concerning infringement.

On July 28, 2000, the court found that there were genuine issues of material fact as to what amount of copper ions constitutes "copper ions in an amount sufficient to degrade" and whether histidine is a "chelator of copper ions." Glaxo Wellcome Inc. v. Genentech, Inc., 107 F.Supp.2d 477, 489 (D.Del.2000). As a result, the court denied Genentech's motion for summary judgment. *See id*.

On October 27, 2000, Glaxo moved for partial summary judgment that Genentech infringes the Page patents arguing that Herceptin and Rituxan infringe Claim 1 of the '403-P patent and Claims 1,2,6 and 9 of the '405 patent. Glaxo contends that the cancer drugs contain the seven elements of the Page patent claims. Genentech responded with a cross-motion for partial summary judgment that it did not infringe on the Page patents. Genentech argues that Herceptin and Rituxan do not contain all the limitations of the Page claims.

On February 7, 2001, Genentech moved for partial summary judgment pursuant to 35 U.S.C. s. 102(g) that Claim 1 of the '403-P patent and Claims 1, 6 and 9 of the '405 patent are anticipated and invalid. Genentech specifically argues that the Page patents are invalid because they are anticipated by Chimeric B72.3, an antibody invented by Celltech, Inc. in conjunction with the National Cancer Institute that is used in treating cancer. Glaxo counters that Chimeric B72.3 does not anticipate the Page patents because the patents do not cover radioimmunotherapy, the central function of Chimeric B72.3. Furthermore, Glaxo argues that the B72.3 antibody is not "therapeutically effective in treating a disease or disorder," and there no teaching of the claimed improvement of the Page patents-an antibody glycosylated by a CHO cell. Finally, Glaxo contends that the Page patented invention was not reduced to practice and even if it was, the use of B72.3 antibody was abandoned, suppressed or concealed.

On February 14, 2001, Genentech moved for partial summary judgment pursuant to 35 U.S.C. s. 102(b) that Claim 1 of the '403-P patent and Claims 1, 6 and 9 of the '405 patent are anticipated and invalid. Genentech argues that the Page patents are invalid because Chimeric B72.3 was a "public use" at least one year prior to the priority date of the Page patents. Genentech also reiterates its position that the treatment of Chimeric B72.3 contains the identical elements as the claims of issue in the Page patents. Glaxo argues in response that there is no evidence of a public use.

On February 14, 2001, Genentech also moved for partial summary judgment of non-enablement of the Page patents. Genentech argues that the Page patents do not enable one of ordinary skill in the art to effectively treat any disease. In particular, Genentech argues that the claims of the Page patents are overly broad and the breadth of enablement in the patent specifications is not commensurate in scope with the claims. Genentech further argues that the unpredictability of the art is evidence that the Page patents are not enabled, and that the quantity of experimentation required by those skilled in the art is undue. Glaxo counters that Genentech's motion is untimely and inappropriate prior to construction of the claims, and that the specifications enable the claimed invention as evidenced by the documented clinical success and testimony by Genentech's expert.

On February 14, 2001, Genentech further moved for summary judgment pursuant to 35 U.S.C. s. 102(e) that Claim 1 of the '403-P patent and Claims 1,2,6 and 9 of the '405 patent are invalid based on the existence of a prior patent. Genentech specifically argues that U.S. Patent No. 6,120,767 (the "Robinson patent") anticipates the Page patents. Glaxo argues in response that the Robinson patent does not anticipate the Page inventions because it does not predate, enable or inherently possess the Page patents.

On February 16, 2001, Genentech moved for partial summary judgment pursuant to 35 U.S.C. s. 112 that the Smith patents are invalid due to indefiniteness. Genentech contends that a potential infringer cannot determine when "copper ions in an amount sufficient to degrade" are present, and that nothing in the patents distinguishes "degradation by the copper ions" from degradation caused by a host of other factors. Genentech further contends that the Smith patents do not convey that the inventors knew the concentration limit at which copper produced degradation. Glaxo counters that the Smith patents are not indefinite.

On February 20, 2001, Genentech moved for partial summary judgment pursuant to 35 U.S.C. s. 102 that the Smith patents are invalid due to anticipation. Genentech argues that every element of the claims of the Smith patents was described in assorted single prior art publications available more than one year prior to the filing date of the Smith patents. Glaxo argues in response that none of the examples of prior art referenced by Genentech anticipate the Smith inventions.

On February 26, 2001, Genentech renewed its motion for summary judgment that Herceptin does not infringe the Smith patents. Specifically, Genentech argues that Glaxo has not identified any facts tending to show that copper causes degradation in Herceptin. Glaxo counters that it is only required to show that Herceptin contains copper ions in an amount sufficient to degrade, not actual degradation.

On March 9, 2001, Genentech moved for summary judgment that Claims 1, 13, 15 and 16 of the '403-S patent and Claim 1 of the '838 patent are anticipated by an immunoglobulin composition known as Gammagard, which has been sold in the United States since 1986.

A three week jury trial is scheduled to begin on April 16, 2001.

II. ***CLAIM CONSTRUCTION***

[1] [2] [3] Claims are construed from the vantage point of a person of ordinary skill in the art at the time of the invention. *Markman,* 52 F.3d at 986. In construing a claim, a court first looks to the intrinsic evidence of record, namely, the claims, the specification and the prosecution history. Pitney Bowes, Inc. v. Hewlett-Packard Co., 182 F.3d 1298, 1309 (Fed.Cir.1999). A court may also look to extrinsic evidence such as inventor testimony, expert testimony dictionaries and learned treatises to assist in the proper construction of a patent claim. *See* Vitronics Corp. v. Conceptronic, Inc., 90 F.3d 1576, 1584 (Fed.Cir.1996)

[4] [5] The starting point in claim construction is the words of the claims themselves. *Id*. Words in the claims are generally given their ordinary and customary meaning unless a patentee clearly sets forth a different definition in the specification or file history. *See Vitronics* at 1582. Therefore, the claims must also be read in view of the specification, of which they are a part. *Markman,* 52 F.3d at 979. As the Federal Circuit has stated:

The specification contains a written description of the invention which must be clear and complete enough to enable those of ordinary skill in the art to make and use it. Thus, the 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. In addition, the prosecution history is often of critical significance in determining the meaning of the claims. *See Markman,* 52 F.3d at 980 ("The prosecution history limits the interpretation of claim terms so as to exclude any interpretation that was disclaimed during prosecution.").

Although the Federal Circuit has held that claims should be read in view of the specification and the prosecution history, the court has repeatedly cautioned against limiting the scope of a claim to the preferred embodiment or specific examples disclosed in the specification. *See, e.g.,* Ekchian v. Home Depot, Inc., 104 F.3d 1299, 1303 (Fed.Cir.1997); Intervet America, Inc. v. Kee-Vet Laboratories, Inc., 887 F.2d 1050, 1053 (Fed.Cir., 1989) ("[L]imitations appearing in the specification will not be read into claims, and ...

interpreting what is meant by a word in a claim 'is not to be confused with adding an extraneous limitation appearing in the specification, which is improper.' ") (citation omitted). In this case, Glaxo and Genentech disagree over the proper construction of nine phrases or terms that are used in the claims of the '403-P, '405, '403-S and '838 patents.

1. ***The Smith Patents***

a. " *immunoglobulin composition of IgG_1 containing copper ions ... comprises*" *and* "*composition comprising IgG_1 and copper ions* "

[6] Genentech contends that the phrases "immunoglobulin composition of IgG_1 containing copper ions ... comprises" of the '403-S patent (Claim 1) FN9 and "a startingcomposition comprising: i) IgG_1 and ii) copper ions" of the '838 patent (Claim 1) FN10 describe a mixture containing a substantial portion of IgG_1 immunoglobulin, which may include other substances such as proteins (including other immunoglobulin types), other organic cell-derived components and non-organic substances.

FN9. Claim 1 of the '403-S patent claims:
In an immunoglobulin composition of IgG_1 containing copper ions in an amount sufficient to degrade the immunoglobulin, wherein the improvement comprises the addition of an amount of a chelator of copper ions sufficient to bind the copper ions present in the composition and protect the immunoglobulin from degradation by the copper ions and thus stabilize the IgG_1 composition

FN10. Claim 1 of the '838 patent claims:
A method of making a stabilized IgG_1 composition comprising adding to a starting composition comprising:

i) IgG_1
ii) copper ions in an amount sufficient to degrade said IgG_1, an amount of a chelator of copper ions sufficient to stabilize said IgG_1 against copper ion mediated degradation, so that said IgG_1 composition is made
In support of its construction, Genentech points to the plain meaning of the claims, arguing that the terms "composition," "comprises" and "comprising" are open-ended terms indicating that the immunoglobulin mixture could include other substances. As intrinsic evidence of the open-ended nature of the terms, Genentech refers the court to certain passages from the '403-S specification, which it argues, make clear that other substances can be included in the mixture. Genentech also refers the court to Genentech, Inc. v. Chiron Corp., 112 F.3d 495 (Fed.Cir.1997), and *Landis on Mechanics of Patent Claim Drafting* as extrinsic evidence defining the term "comprising." Finally, as evidence of the plain meaning of the term "composition," Genentech urges the court to consider the Oxford English Dictionary, which defines "composition" as "a substance or preparation formed by combination or mixture of various ingredients."

Glaxo counters that the phrases convey a different plain and ordinary meaning to one of skill in the art. That is, they describe a composition containing only IgG_1 immunoglobulin. As support for its construction, Glaxo points to the prosecution history. In particular, Glaxo argues that when the applicants amended the

phrase "composition comprising an IgG_1 immunoglobulin" to read "composition of IgG_1," they reduced the parts of the composition from plural to singular. Glaxo contends that claims cannot be construed to include subject matter surrendered by limiting claim amendments, and thus, Claim 1 of the '403-S patent and all dependant claims require that the "composition of IgG_1" contain only IgG_1 immunoglobulin. As such, the essence of the dispute over these phrases is whether the immunoglobulin composition can contain other substances in addition to IgG_1.

As a preliminary matter, the court finds that the term "comprises" in Claim 1 of the '403-S patent refers to the "improvement," not the "immunoglobulin composition." As such, "comprises" cannot possibly indicate whether the composition can include substances other than IgG_1. The terms "comprising" and "composition," however, do relate to the immunoglobulin composition.

When interpreting the plain meaning of the phrases, the court looks to the traditional meanings of their terms. In construing such terms, the court recognizes that "comprising" is traditionally "a term of art used in claim language which means that the named elements are essential, but other elements may be added and still form a construct within the scope of the claim." Chiron, 112 F.3d at 497. The court further recognizes that a "composition" is traditionally a combination of two or more substances, and that IgG_1 is a protein constituting a single substance. *See e.g.* Diamond v. Chakrabarty, 447 U.S. 303, 100 S.Ct. 2204, 65 L.Ed.2d 144 (1980).

The inventors did not set forth alternative definitions for these terms in the specifications or prosecution histories of the '403-S or '838 patents. Furthermore, the fact that the inventors removed the term "comprising" from Claim 1 of the '403-S patent does not change the plain meaning of the term "composition," which remains in the final version of the claim. Moreover, if the court were to adopt the construction of the '403-S claims put forth by Glaxo, Claim 1 would contradict Claim 1 of the '838 patent, which retains the term "comprising" and claims the process for producing the compositions described in '403-S patent. Such a construction would be inconsistent.

In light of these findings, the court concludes that the terms "comprising" and "composition" must be construed according to their plain meanings. *See* Vitronics, 90 F.3d at 1582 (holding that words in claims are generally given their ordinary and customary meaning unless the patentee clearly sets forth a different in the specification or file history). As a result, the phrases "immunoglobulin composition of IgG_1 containing copper ions" of the '403-S patent and "a starting composition comprising: i) IgG_1 and ii) copper ions" of the '838 patent describe a mixture containing IgG_1 immunoglobulin that can include other substances.

b. "*copper ions in an amount sufficient to degrade*"

[7] In *Glaxo,* this court construed the phrase "copper ions in an amount sufficient to degrade" to require enough copper ions to degrade. *See* 107 F.Supp.2d at 487. In construing the phrase according to its plain meaning, the court rejected Genentech's argument that the phrase requires a specific numerical amount of copper ions to be present in the starting composition. *See id.*

Genentech now argues that the court's interpretation requiring enough copper ions to degrade imposes an affirmative limitation on Claims 1 of the '403-S and '838 patents. Genentech specifically argues that the copper ions must actually degrade the accused composition when the copper ions present in the composition are not bound by the chelator. That is, the copper ions must have a demonstrable effect. Glaxo counters that

the phrase requires enough copper ions to degrade by cleaving the IgG_1 immunoglobulin into fragments.

After reviewing the specification and file histories of the patents, the court sees no reason to modify the plain meaning construction of the phrase it set forth in *Glaxo*. As a result and for the reasons stated in *Glaxo,* the phrase "copper ions in an amount sufficient to degrade" requires enough copper ions to degrade IgG_1 immunoglobulin.

c. "*degradation by the copper ions*" and "*copper ion-mediated degradation*"

[8] Genentech argues that the phrases "degradation by the copper ions" of the '403-S patent (Claims 1 and 16) FN11 and "copper ion-mediated degradation" of the '838 patent (Claim 1) require a rate of copper-induced degradation relative to peak C that is higher than the background degradation rate at the conditions tested. "Peak C" is a peak of degradation formed by the major degradation product of an antibody which has a molecular weight of approximately 50k. In the specification, the inventors use peak C as a scale against which other rates of degradation are measured. "Background degradation" is the degradation that naturally occurs absent the introduction of copper ions. In support of its construction, Genentech points to patent examples, Glaxo documents and testimony of the Smith inventors as evidence that the Smith patent claims require a higher degradation rate.

FN11. Claim 16 of the '403-S patent claims:
A stabilized immunoglobulin composition comprising an IgG_1 and copper ions, wherein the copper is present in an amount sufficient to degrade the immunoglobulin, together with an amount of a chelator of copper ions sufficient to bind the copper ions present in the composition and protect the immunoglobulin from degradation by the copper ions

Glaxo argues in response that the term "degradation" conveys its plain and ordinary meaning to one of skill in the art. That is, "degradation" is any copper ion-mediated degradation of an IgG_1 antibody in storage. The essence of the dispute over these phrases, therefore, is whether the invention requires that the pre-chelator immunoglobulin composition exhibit a minimum rate of degradation greater than the rate of background degradation.

In support of its position, Genentech first argues that Example 1 of the '838 patent reveals that the degradation rate in the pre-chelator immunoglobulin composition must be more than the background rate. In the example, the inventors show that the composition with no additives degrades at 12% of peak C when stored at +37C. This is the background degradation rate. With the addition of copper ions, the composition degrades at 28% of peak C. When EDTA, a chelator of copper ions, is added to the composition, it degrades at less than 1% of peak C. The example demonstrates that the introduction of a chelator can reduce degradation to negligible levels, but it does not expressly or implicitly require that the pre-chelator composition degrade at a rate higher than the background rate.

Genentech next argues that testimony of Dr. Smith reveals that the rate of copper ion-mediated degradation required by the Smith patents is greater than that of background degradation. In a deposition, Dr. Smith was asked, "[s]o it was your understanding that copper-induced degradation caused a uniquely high level of degradation ...?" Dr. Smith responded, "[y]es our experiments indicated that copper gave vast amounts of this-of degradation." Dr. Smith's testimony reveals that copper degrades the immunoglobulin composition at

greater rate, but it does not establish a patent requirement that the pre-chelator composition degrade at a rate higher than the background rate.

Finally, Genentech argues that recorded data from experiments done by the inventors while working on the Page patents reveal a required minimum degradation rate. Genentech specifically contends that "[i]n experiments designed to look at the effect of EDTA in inhibiting copper induced cleavage, baseline peak C in the control sample held at +37C was approximately 12%...." Genentech points out that the copper mediated degradation of the '403-S example was 12%. For reasons previously stated with regard to Example 1, the court finds that the data do not expressly or implicitly require that the pre-chelator composition degrade at a rate higher than the background rate.

After reviewing the specification, the testimony of Dr. Smith and the results of the Page experiments, the court finds that the evidence set forth by Genentech demonstrates that copper often degrades the immunoglobulin composition at a high rate relative to peak C, but it does not confirm that the Smith patents require a degradation rate above the background degradation rate. In short, the specification examples do not create implicit claim limitations. Thus, the court concludes that the phrases should be construed accordingto their plain meaning, and therefore interprets the phrases "degradation by the copper ions" of the '403-S patent and "copper ion-mediated degradation" of the '838 patent to require degradation of the immunoglobulin composition by copper ions.

d. "*chelator of copper ions sufficient ... to protect ... [and] stabilize*" and "*chelator of copper ions sufficient to stabilize*"

[9] Genentech argues that the phrases "an amount of a chelator of copper ions sufficient to bind the copper ions ... protect the immunoglobulin ... [and] stabilize the ... composition" of the '403-S patent (Claims 1) and "an amount of chelator of copper ions sufficient to stabilize [the] ... composition" of the '838 patent (Claim 1) require that the "chelator of copper ions" not simply bind copper ions, but also protect and stabilize the composition. That is, the chelator must compete with the antibody to bind the copper, thereby preventing the copper from binding with and eventually degrading the antibody.

Glaxo counters that the phrases convey their plain and ordinary meaning to one of skill in the art in that the chelator must be an agent added to the composition that is capable of binding the copper ions present, and must reduce, eliminate or retard copper ion-degradation of the antibody. As such, the essence of the dispute over these phrases is whether the claims require a specific method of protection and stabilization of the composition.

In support for its position, Genentech refers the court to the patent examples and expert reports. Genentech first contends that Examples 1-9 of the '403-S patent define the method of protection required by the claims. As an example, Genentech refers to the following passage form Example 1 of the '403-S patent:

The ... table shows the approximate stoichiometry of binding of Cu.sup.2+ by mM-EDTA and 2 mM-citrate and the contributory effect of pH. 2 mM-EDTA in phosphate buffered saline, pH 7.2, is the most effective suppressing copper induced cleavage of Campath-1H. An approximate 1:1 stoichiometry of binding is indicated at pH 7.2. Copper concentrations in excess of 2mM cause cleavage of CAMPATH-1H (anti-CDw52 antibody) in 2 mM EDTA

This passage explains that EDTA, a type of chelator, effectively suppresses degradation by binding the

antibody, but it does not modify or explain the nature of the binding process.

Genentech also contends that Dr. Kerr's report and the Tranter Report, two expert reports noting that antibodies are known to have several sites capable of binding copper, each with different binding affinities, support its construction that the chelator must effectively compete with copper ions present in the antibody in order to "protect" and "stabilize" the antibody composition. The court finds that reports do not require that it read this limitation into the phrase "chelator of copper ions."

After reviewing the proposed constructions, the court finds that the phrases should be interpreted according to their plain meaning, and therefore construes the phrases "an amount of a chelator of copper ions sufficient to bind the copper ions ... protect the immunoglobulin ... [and] stabilize the ... composition" of the '403-S patent and "an amount of chelator of copper ions sufficient to stabilize [the] ... composition" of the '838 patent to require that the "chelator of copper ions" bind copper ions, and that such bonds protect and stabilize the antibody composition.

e. "*protect the immunoglobulin from degradation and thus stabilize the IgG_1 composition*" and "*so that said stabilization (sic) composition is made*"

Genentech argues that the phrases "protect the immunoglobulin from degradation and thus stabilize the IgG_1 composition" of the '403-S patent (Claim 1) and "so that said stabilization (sic) composition is made" of the '838 patent (Claim 1) require copper-mediated degradation that is significantly reduced by the addition of chelator. Genentech contends that in order for the immunoglobulin composition to be stabilized, the copper mediated degradation that would otherwise have occurred absent a chelator of copper ions must be substantially prevented. In support of its construction, Genentech refers the court to the specification, the file history and the inventors' testimony as evidence that the terms "protect" and "stabilize" require nearly complete prevention of the degradation.

Glaxo argues in response that the phrases convey their plain and ordinary meaning to one of skill in the art in that they require a reduction, elimination or retardation of copper ion-mediated degradation. Therefore, the essence of the dispute over these phrases is whether the terms "stabilize" and "protect" require that the chelator substantially prevent degradation of the composition, or simply reduce such degradation.

In support of its construction, Genentech first refers the court to an excerpt from Example 1 of the '403-S specification. In describing the results of the experiment, the excerpt states that "[t]hese results demonstrate that copper enhances the degree of degradation of the antibody relative to the control. The addition of EDTA virtually eliminates degradation whilst the other metal ion chelator 1,10-phenanthroline reduces degradation to a considerable extent." The excerpt makes clear that two chelators, EDTA and 1,10-phenanthroline, nearly prevent degradation, but the invention is not limited to EDTA and 1,10-phenanthroline. Such results cannot be presumed for all chelators of copper ions. Thus, Example 1 does not create a limitation that the chelators virtually prevent degradation.

Genentech also relies on deposition statements made by Dr. Riveros, one of the Smith inventors, in support of its construction. In describing decreases resulting from the addition of a protease inhibitor to the composition, Dr. Riveros stated that "it's not something that is drastic like it is the effect of EDTA and copper." Genentech argues that Dr. Riveros' characterization of the stabilizing effect of EDTA on copper as drastic shows that such effect is required by the patent claims. Again, the Smith patents are not limited to the chelator EDTA. Therefore, the statement does not reveal a requirement that chelators substantially

prevent degradation of the composition.

Genentech next points to Dr. Riveros' answer to a question by opposing counsel, in which opposing counsel asked "[s]o it's your understanding that when it's less than one percent change in degradation or showing one percent degradation that that is because of the detection method?" Dr. Riveros responded, "I understand the method has variations which are in-built in the method and one-percent is really insignificant. You can see the increase produced by copper can be over a hundred percent degradation." Genentech contends that this testimony distinguishes the stabilization and protection required by Smith patents from "insignificant" protection. After reviewing the context of that statement, the court finds that Dr. Riveros responded to the second part of a compound question. That is, he was speaking to degradation rates, not reduction rates. This is evident in the second part of Dr. Riveros' response where he refers only to "one hundred percent" degradation. As such, the response does not reveal a limitationthat chelators substantially prevent degradation of the composition.

After reviewing the parties' proposed constructions, the court concludes that the phrases should be construed according to their plain meaning. The term "stabilizer" is defined as "[a]ny substance that tends to keep a compound, mixture or solution from changing form or chemical nature. Stabilizers may retard a reaction rate [or] ... preserve a chemical equilibrium ...." Richard J. Lewis Sr., *Hawley's Condensed Chemical Dictionary* 1042 (13th ed.1997). The specification and the examples therein show dramatic reductions in degradation, but they do not modify the plain meaning of "stabilize" or "protect," and they certainly do not establish a required amount of stabilization or protection. As such, the court construes the phrases "protect the immunoglobulin from degradation and thus stabilize the IgG_1 composition" of the '403-S patent and "so that said stabilization (sic) composition is made" of the '838 patent to require that the chelator reduce degradation.

2. *The Page Patents*

a. " *therapeutically effective ... effective in treating* "

[10] Genentech argues that the phrases "therapeutically effective" and "effective in treating" of Claims 1 of the Page patents FN12 restrict the claims to a CHO-glycosylated antibody that has proven to be therapeutically effective when previously expressed in a different cell line. In support of its construction, Genentech contends that the Jepson format of both claims requires that the "improvement" claimed be limited by the preamble of the claim. Genentech also refers the court to papers submitted during an interference proceeding as evidence that the invention only includes antibodies previously shown to be effective. Finally, Genentech lists a number of reasons why a construction requiring that effectiveness depend on the antibody's capacity to have an effector function is unsupported and contrary to the plain meaning of the phrases.

FN12. Claim 1 of the '403-P patent claims:
In a method for treating a human suffering from a disease or disorder comprising administering a therapeutically effective amount of a whole glycosylated recombinant human chimeric or CDR-grafted or bispecific antibody effective in treating said disease or disorder in said human, wherein the improvement comprises an antibody glycosylated by a Chinese hamster ovary cell.

Claim 1 of the '405 patent claims:
In a method for treating a human suffering from cancer by administering a therapeutically effective amount of a whole glycosylated recombinant human, chimeric, CDR grafted or bispecific antibody effective in treating said cancer, wherein the improvement comprises an antibody glycosylated by a Chinese hamster ovary cell.

Glaxo counters that the phrase "therapeutically effective" describes an amount of CHO-glycosylated antibody that provides a therapeutic benefit when administered to a human patient, not treatment with antibodies derived from a different cell line. Glaxo argues that there is no basis in the patents or file histories for Genentech's proposed construction. Glaxo further argues that Genentech has misrepresented Glaxo's position in the interference proceeding papers. In light of these arguments, the essence of the dispute over these phrases is whether antibodies derived from Glaxo's invention must have demonstrated a therapeutic effect when previously produced by a non-CHO cell line.

During the prosecution of the '403-P patent, the PTO advised the applicants in the August 5, 1994 Office Action that the application was directed at patentably distinct species, such as vaculitis, lupus, cancer and infectious disease. The examiner instructed the applicants to elect a single species for prosecution on the merits in the event no generic claim was allowed. Rather than select a single species, the applicants submitted Claim 1 of the '403-P patent in Jepson format claiming an "improvement."

[11] [12] A claim drafted in the Jepson format "allows a patentee to use [a] preamble to recite 'elements or steps of the claimed invention which are conventional or known' " Rowe v. Dror, 112 F.3d 473, 479 (Fed.Cir.1997) (quoting 37 C.F.R. 1.75e (1996)). When a patentee uses the Jepson format, the claim preamble defines the context of the claim. *See id*. Moreover, "if [a] claim preamble is 'necessary to give life, meaning, and vitality' to the claim, then the claim preamble should be construed as if in the balance of the claim." Pitney Bowes, Inc. v. Hewlett-Packard, 182 F.3d 1298, 1305 (Fed.Cir.1999) (citations omitted).

After reviewing claims and the file history, the court concludes that Claims 1 of the Page patents are drafted in the Jepson format, and the plain language of the claims reveals that a portion of each preamble was previously known. The known portions, however, are limited to the phrases "[i]n a method for treating human suffering or disease" and "[i]n a method for treating cancer." The remainder of each preamble relates to CHO-glycosylated antibody treatment.

A broader construction rendering no portion of the preamble previously "known" would bring any method of treatment within the claim. This construction is inconsistent with the examiner's instructions in the August 5, 1994 Office Action rejecting the original broad multi-species claim. A narrower construction rendering the entire preamble "known" would negate the meaning of the term "wherein." The plain meaning of "wherein" shows that CHO-glycosylated antibodies contribute to the effect of the treatment described in the preambles. The court, therefore, concludes that the claims require a previously known method for treating human diseases, disorders or cancer, but the phrases "therapeutically effective" and "effective in treating" describe treatment with CHO-glycosylated antibodies, not previous therapy with antibodies derived from non-CHO cell lines.

b. *CDR-grafted*

[13] Genentech argues that the term "CDR-grafted" of Claims 1 of the Page patents describes a particular type of recombinant antibody in which all six CDRs are transferred in their entirety from a non-human antibody onto a single human framework. The CDRs are six specific regions in the portion of the antibody corresponding to the arms of the "Y" shape that form the antigen binding site. Genentech contends that its proposed construction is supported by the specification and the examples of CDR-grafted antibodies referenced therein.

Glaxo argues in response that the term "CDR-grafted" describes a recombinant antibody where individual non-human CDRs or the amino acids therein have been altered before grafting into a human antibody framework region. Moreover, Glaxo points out that the specification does not state a specific number of CDRs, nor does it include the term "completely" in conjunction with "CDR-grafted." Thus, Glaxo contends that partial replacement is sufficient to satisfy the patent claims. In light of these proposed constructions, the essence of the dispute over this term is whether an antibody must have six complete non-human CDRs to be considered "CDR-grafted."

In support of its construction, Genentech refers the court to a portion of the specification describing a CDR-grafted antibody in a murine cell context as an antibody "where the murine constant domains and the murine framework regions are replaced by equivalent domains and regions of human origin." Genentech argues that this passage indicates that the CDRs are replaced by corresponding portions from a non-human antibody. Genentech further refers the court to a portion of the specification describing a CDR-grafted antibody as a "composite antibody, wherein parts of the hypervariable region in addition to the CDRs are transferred to the human framework." Genentech contends that this passage requires that a CDR-grafted antibody contain "parts" of a non-human hypervariable region along with all six non-human CDRs. Glaxo counters that the term "parts" refers to the CDRs, and as a result, CDR-grafted antibodies may include less than six complete non-human CDRs.

After reviewing the disputed passage of the specification, the court concludes that the term "parts" refers to the hypervariable region and not the CDRs. Moreover, the article "the" modifying CDRs makes the term "CDRs" inclusive of all CDRs. The court, therefore, finds that one skilled in the art would understand the passage to describe the presence of all CDRs in addition to other parts of the hypervariable region. As such, the court construes the phrase "CDR-grafted" to describe a recombinant antibody where all six CDRs have been replaced with complete non-human CDRs.

c. " *chimeric* "

[14] Genentech argues that the term "chimeric" of Claims 1 of the Page patents describes an antibody in which only the non-human constant domains have been replaced by equivalent domains of human origin. In support of its proposed construction, Genentech refers to examples of chimeric antibodies set forth in the specification as prior art consistent with its construction.

Glaxo counters that the term "chimeric" describes an antibody that derives its amino acid sequences from two genetically distinct parents. Glaxo contends that the term does not require that only the constant domains be replaced. Glaxo points to a portion of the specification stating that "chimeric antibodies may have one or more further modifications" as support for its construction. Therefore, the essence of the dispute over the term "chimeric" is whether chimeric antibodies are only those antibodies that have imported human constant domains and no other modifications.

In the context of murine cell antibody production, the specification explains that chimeric antibodies are antibodies where "the murine constant domains *only* are replaced by equivalent domains of human origin" (emphasis added). The specification, however, also explains that "chimeric antibodies may have one or more further modifications to improve antigen binding ability or to alter effector functioning." The court will construe the term "chimeric" so that it is consistent with both portions of the specification. Thus, "chimeric" describes an antibody in which the non-human constant domains are replaced by equivalent domains of human origin, and any additional modifications are only for the purposes of improving the antigen binding ability or altering the effector functioning.

d. " *whole glycosylated* "

[15] Genentech contends that the phrases "whole glycosylated recombinant human chimeric or CDR grafted or bispecific antibody" of the '403-P patent (Claim 1) and "whole glycosylated recombinant human, chimeric, CDR-grafted or bispecificantibody" of the '405 patent (Claim 1) describe an antibody that exhibits complete glycosylation in that its carbohydrate chain terminates with the appropriate galactose sugar. Genentech argues that the plain meaning of the phrase requires that "whole" modify "glycosylated," and that use of "whole" as an adverb is grammatically correct. Genentech explains that the specification indicates the importance of having glycosylation in the correct configuration for maintaining all of the antibody's binding properties.

Glaxo argues in response that "whole" modifies "antibody," and if "whole" had been intended to modify "glycosylated," the phrase would have read "wholly glycosylated." Glaxo further argues that the specification does not support Genentech's proposed construction.

In support of its construction, Genentech points to a pending interference proceeding where Glaxo explained that "the adjective 'whole' modifies 'glycosylated ... antibody' and conveys the meaning of an antibody having both constant (Fc) and variable regions (Fab) regions which is glycosylated on the Fc region as opposed to being glycosylated solely on the Fab thereof." Genentech contends that this statement shows that "whole" modifies "glycosylated." The court, however, finds that this statement supports Glaxo's construction. The statement labels "whole" as an adjective, not an adverb as advocated by Genentech. Moreover, the statement explains that the phrase "whole glycosylated ... antibody" conveys the meaning of an antibody having all necessary regions. That is, it conveys a whole antibody.

After reviewing the parties' proposed constructions, the court concludes that the term "whole" should be construed according to its plain meaning to describe "antibody," and not "glycosylation." As a result, the phrases "whole glycosylated recombinant human, chimeric or CDR-grafted or bispecific antibody" of the '403-P patent and "whole glycosylated recombinant human, chimeric, CDR-grafted or bispecific antibody" of the '405 patent describe a whole recombinant human, chimeric, CDR-grafted or bispecific antibody that is glycosylated.

III. *SUMMARY AND CONCLUSION*

With regard to the Smith patents, the court concludes that the phrases "immunoglobulin composition of IgG_1 containing copper ions ... comprises" and "a starting composition comprising: i) IgG_1 and ii) copper ions" describe a mixture containing IgG_1 immunoglobulin that can include other substances. The phrase "copper ions in an amount sufficient to degrade" requires enough copper ions to degrade IgG_1 immunoglobulin. The

phrases "degradation by the copper ions" and "copper ion-mediated degradation" require degradation of the immunoglobulin composition by copper ions. The phrases "an amount of a chelator of copper ions sufficient to bind the copper ions ... protect the immunoglobulin ... [and] stabilize the ... composition" and "an amount of chelator of copper ions sufficient to stabilize [the] ... composition" require that the chelator bind copper ions, and that such bonds protect and stabilize the antibody composition. Finally, the phrases "protect the immunoglobulin from degradation and thus stabilize the IgG_1 composition" and "so that said stabilization (sic) composition is made" require that the chelator reduce degradation.

With regard to the Page patents, the court concludes that the phrases "therapeutically effective" and "effective in treating" describe treatment with CHO-glycosylated antibodies. The term "CDR-grafted" describes an antibody where non-human constant domains and framework regions, including CDRs, are all replaced by equivalent domains and regions of human origin. The term "chimeric" describes an antibody in which the non-human constant domains are replaced by equivalent domains of human origin, and any additional modifications are only for the purposes of improving the antigen binding ability or altering the effector functioning. Lastly, the phrases "whole glycosylated recombinant human, chimeric or CDR-grafted or bispecific antibody" and "whole glycosylated recombinant human, chimeric, CDR-grafted or bispecific antibody" require a whole recombinant human, chimeric, CDR-grafted or bispecific antibody that is glycosylated.

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