United States District Court,
S.D. New York.

EVANS MEDICAL LTD., Medeva PLC, SmithKline Beecham Biologicals S.A., SmithKline Beecham Biologicals Manufacturing S.A. and SmithKline Beecham Corporation,
Plaintiffs.
v.
AMERICAN CYANAMID COMPANY, Takeda Chemical Industries, Ltd. and American Home Products Corporation,
Defendants.
AMERICAN CYANAMID COMPANY, Takeda Chemical Industries, Ltd. and American Home Products Corporation,
Counterclaim Plaintiffs.
v.
EVANS MEDICAL LTD., Medeva PLC, SmithKline Beecham Biologicals S.A., SmithKline Beecham Biologicals Manufacturing S.A. and SmithKline Beecham Corporation,
Counterclaim Defendants.

No. 96 Civ. 3529(WCC)

June 10, 1998.

Patentee brought action for infringement of patents for acellular antigens and vaccines for pertussis. Parties filed motions for summary judgment and various other pretrial motions. The District Court, William C. Conner, Senior District Judge, held that: (1) patents were not infringed, and (2) patents were valid.

Ordered accordingly.

5,237,052, 5,438,120, 5,648,080. Valid and not infringed.

Richards & O'Neil, LLP, New York City (Edward L. Powers, of counsel), Robins, Kaplan, Miller & Ciresi L.L.P., Atlanta, GA, (A. James Anderson, Brent J. Kaplan, of counsel), Robins, Kaplan, Miller & Ciresi L.L.P., Minneapolis, MN (Michael V. Ciresi, Ronald L. Schutz, of counsel), Popovich & Wiles, PA, Minneapolis, MN (Thomas E. Popovich, Patrick J. O'Connell, of counsel), for Plaintiffs Evans Medical Ltd. & Medeva PLC.

Briccetti & Calhoun, White Plains, NY (Vincent L. Briccetti, of counsel), Covington & Burling, Washington, DC (William D. Iverson, Michael A. Dawson, Adriana S. Luedke, of counsel), for Plaintiffs SmithKline Beecham Biologicals S.A., SmithKline Beecham Biologicals Mfg. S.A. and SmithKline Beecham Corp.

Kenyon & Kenyon, New York City (Paul H. Heller, George E. Badenoch, Estelle J. Tsevdos, Frederick H. Rein, of counsel), for Defendants and Counterclaim Plaintiffs American Cyanamid Co., Takeda Chemical Industries, Ltd. and American Home Products Corp.

OPINION AND ORDER

WILLIAM C. CONNER**, Senior District Judge.**

This is an action for alleged infringement of three United States patents on acellular antigens and vaccines for pertussis, or whooping cough. The patents were issued in the name of Pavel Novotny on applications filed by his employer, Burroughs Wellcome Foundation Ltd. ("Burroughs Wellcome"). Plaintiff Medeva PLC ("Medeva") purchased the vaccine business of Burroughs Wellcome and the patents were assigned to Medeva's subsidiary, plaintiff Evans Medical Ltd. ("Evans"), which granted an exclusive license under the patents to plaintiff SmithKline Beecham Biologicals S.A. ("SmithKline"). Plaintiffs charge that the patents are infringed by a composite "DTaP" vaccine for diphtheria, tetanus and pertussis sold in the United States by defendants American Cyanamid Co. ("American Cyanamid") and American Home Products Corp. ("American Home Products") under the brand name ACEL-IMUNE(R), and incorporating acellular pertussis antigens produced in Japan by defendant Takeda Chemical Industries Ltd. ("Takeda"). The action is before the Court on a welter of pretrial motions.

Defendants have moved: (1) for a ruling by the Court under Markman v. Westview Instruments, Inc., 517 U.S. 370, 116 S.Ct. 1384, 134 L.Ed.2d 577 (1996), construing the patent claims and for summary judgment that the claims, as so construed, have not been infringed by defendants' accused vaccine; (2) for summary judgment that the patents in suit are invalid because their specifications (all of which are identical) fail to disclose the best mode of practicing the invention known to the patentee at the time the applications were filed, as required by 35 U.S.C. s. 112; (3) for summary judgment that the patents are invalid under 35 U.S.C. s. 102 because the claimed inventions were anticipated by a prior patent of defendant Takeda and by the prior sale and use of Takeda's antigen in this country; (4) for summary judgment that the patents are invalid under 35 U.S.C. s.s. 102 and 103 because the claimed inventions were anticipated by or obvious in view of a March 1985 article co-authored by Novotny, Juan Montaraz (a doctoral student under Novotny's supervision), and Juraj Ivanyi; (5) for an order *in limine* excluding certain testimony of plaintiffs' patent law expert Gerald Bjorge; and (6) for an order *in limine* excluding certain testimony of Tom Bozzo or any other witness regarding FDA approval of defendants' vaccine.

Plaintiffs have moved: (1) for partial summary judgment that the patents in suit are not anticipated by the prior patents and publications cited by defendants; (2) for partial summary judgment that, for purposes of determining whether the patent specification satisfies the best mode requirement of 35 U.S.C. s. 112, the January 1990 deposit in the European Collection of Animal Cell Cultures of a hybridoma which secretes a monoclonal antibody used in purification of the patented antigen relates back to the May 1, 1985 filing of the parent U.S. application; (3) for an order pursuant to 35 U.S.C. s. 256 directing correction of the patents in suit to add Montaraz as an inventor; (4) for an order compelling defendants to return certain inadvertently produced documents; (5) for an order *in limine* excluding the expert testimony of Dr. Alison Weiss; and (6) for an order *in limine* excluding evidence at trial of related litigation in the United Kingdom.

Following a background discussion, the motions will be discussed serially. Unless otherwise indicated, all of the background facts recited herein are undisputed.

BACKGROUND

Development of pertussis ***vaccines***

Pertussis, or whooping cough, is one of the most common serious diseases of infants, with an estimated 50 million cases annually causing 600,000 deaths. A vaccine introduced in the late 1940's strikingly reduced the incidence of the disease in developed countries where large scale immunization programs were undertaken. But that vaccine was prepared from chemically killed whole cells of *Bordetella* pertussis *("B.* pertussis"*),* the bacterium which causes whooping cough, and caused serious side effects in a significant number of those inoculated, including fever and persistent screaming. This resulted in curtailment of the immunization programs and a concomitant increase in the incidence of the disease.

The vaccines involved in the present case are acellular, incorporating not whole bacterial cells but selected proteinaceous material extracted from the outer membrane of *B.* pertussis bacteria by, for example, treatment with an amino acid solution. This breaks down the proteins of the outer membrane into fragments comprising long strands of amino acids connected in a sequence which determines the properties and behavior of the material. The extracted material is then subjected to a series of purification steps designed to increase the concentration of a particular protein, now known as pertactin, which has been found to have excellent immunogenic effect against *B.* pertussis infection. The pertactin strands have a number of active sites or epitopes which are recognized by the defensive white blood cells, or B lymphocytes, of the inoculated patient as characteristic of *B.* pertussis bacteria, thereby stimulating the lymphocytes to produce antibodies which will attack *B.* pertussis bacteria in the event of a later infection and provide effective immunity without the serious side effects of whole cell vaccines. Acellular antigens containing pertactin are currently in widespread use in vaccines for *B.* pertussis, frequently in composite DTaP vaccines designed to immunize against diphtheria and tetanus as well.

The patents in suit

Plaintiffs have sued on three U.S. patents: No. 5,237,052 (the " '052 patent"), No. 5,438,120 (the " '120 patent") and No. 5,648,080 (the " '080 patent"). (Exhs. 1-3 to Defs.' Motions for Summ. J. FN1) All three patents have identical specifications and are based upon the same parent U.S. application, Serial No. 929,257, filed May 1, 1985, which claims priority based upon the United Kingdom specification Serial No. 8,412,207, filed May 12, 1984.

FN1. Unless indicated otherwise, all citations to exhibits refer to those contained in the four-volume "Exhibits to Defendants' Summary Judgment Motions."

The patents were issued in the name of Pavel Novotny and were based in part on work done in the laboratory of Burroughs Wellcome by Novotny's student assistant, Juan Montaraz, who used the research as the basis for his doctoral thesis and as the subject of an article entitled "Identification of a 68-Kilodalton Protective Protein Antigen from *Bordetella bronchiseptica,* " published in the March 1985 issue of INFECTION AND IMMUNITY in the names of Montaraz, Novotny and Juraj Ivanyi (the "Montaraz et al. article").

The common specification of the patents in suit identifies the desired antigen as "proteinaceous material associated with adenylate cyclase activity" (referred to by the acronym ACAP) and as having an isoelectric point ("pI") FN2 of "about 7," "a relative molecular weight of about 67,000 to 73,000, particularly 69,000" FN3 and a "proline:glutamic acid ratio of about 1:1." FN4 The specification discloses a preferred process of preparing the patented antigen. The first step of this process, denominated "Example 1," involves incubating

a culture of *B*. pertussis cells with an aqueous amino acid buffer with a pH of about 3 for 10-20 hours at 30-45 (deg.) C. The mixture is centrifuged at 100,000g to separate the cells and particulate matter. The supernatant extract is then subjected to a multi-step purification process, the several steps being respectivelydenominated "Examples 2(a), 2(b) and 3."

FN2. Each protein has a characteristic net electric charge which varies with the pH of its ambient solution. Most proteins are positively charged in low pH (acidic) solutions and negatively charged in high pH (alkaline) solutions. The isoelectric point (pI) of a protein is the pH at which it has no net electric charge. If its pI is 7, its net electric charge in a neutral solution is zero.

FN3. Molecular weight is measured in daltons and is approximately proportional to the number of protons and neutrons in the molecule. Because proteins are long-chain molecules, their molecular weights are comparatively large. A protein with a molecular weight of 69,000 daltons is often referred to as a 69 kDa (or simply 69k) protein. The approximate or "relative" molecular weight of a protein may be determined by polyacrylamide gel electrophoresis ("PAGE"). In this process, the protein material is dissolved in sodium dodecyl sulphate ("SDS") which unfolds the protein molecules and breaks their linkages to other molecules. The negatively charged SDS ions bind with the protein molecules to form complexes having a net negative charge proportional to the mass of the protein. This solution is placed in a well at the top of the polyacrylamide gel, and electrodes of opposite polarity are applied at opposite ends of the gel. The negatively charged SDS-protein material moves toward the positive end a distance proportional to its molecular weight. Its position is visualized by staining with, *e.g.,* Coomassie Blue dye. Other materials of known molecular weight are subjected to electrophoresis in the same gel field to provide markers for calibration of the field.

FN4. Proline and glutamic acid are two of the amino acids which make up the protein's molecular chain.

"Example 2(a)" consists of separating the fractions of the extracted outer membrane material by chromatography in a DEAE-Trisacryl column.FN5 The retained protein molecules are eluted from the column by flushing with an 0.2M NaCl buffer.

FN5. Chromatography is the process of separating the component molecules of a mixture by passing it through a column filled with a permeable material to which selected molecules of the mixture are bound. The molecules are later released and eluted from the column by passing a buffering solution through the column. Diethylaminoethyl cellulose ("DEAE") Trisacryl is a column material which selectively binds ACAP molecules.

"Example 2(b)" consists of preparative flat-bed isoelectric focusing ("IEF") in a granulated gel.FN6 The eluate from Example 2(a) is embedded in the gel. After electrophoresis, the material which collects in the band at a pI of 7 is scraped from the field and dissolved in distilled water. The gel suspensions are placed in columns and eluted with an 0.2M ammonium bicarbonate buffer at pH 7.0 to produce a gel-free eluate.

FN6. IEF separates molecules on the basis of their net electrical charge (pI) by electrophoresis. The liquid containing the proteins to be separated is placed on a flat gel bed having electrodes of opposite polarity

applied at its opposite sides to create an electrical gradient across its width. The various proteins migrate across the gel to the position which corresponds to their respective pIs and thus congregate in bands which are spaced across the width of the gel bed and which are visualized by staining with a dye.

"Example 3" consists of further purification of the separated protein material in an immunosorbent chromatographic column charged with "a monoclonal immunoglobulin specific for ACAP." In the parent U.S. application filed May 1, 1985, the monoclonal antibody employed in this final purification step was not otherwise described. It was not until September 21, 1992, over seven years after the filing of the application, and over eight years after the claimed U.K. priority date, that a fifth-generation continuation of the parent U.S. application was amended to add the following reference for identification of the key monoclonal antibody:

The hybridoma which secretes the monoclonal immunoglobulin was deposited under the Budapest Treaty at the European Collection of Animal Cell Cultures, Porton Down, United Kingdom on Jan. 5, 1990 under accession number 90010501. FN7

FN7. Where biological material cannot be taxonomically described, the U.S. Patent and Trademark Office accepts the deposit of physical samples of the material in a publicly accessible depository in satisfaction of the disclosure requirement of 35 U.S.C. s. 112. *See* 37 C.F.R. s.s. 1.801-1.809.

(Exh. 64.)

As the final step in the process of preparation described in the patent specification, denominated "Example 4," the purified ACAP is cultured in a liquid medium containing 2% agar and 5% horse blood for 48 hours at 36-37 (deg.)>> C while agitating to provide a gas exchange rate of 20-40 (mu) M oxygen/hr. The liquid cultures are then used to inoculate the medium in a glass fermentor, with the pH maintained at 7.6 by the controlled addition of 2M HCl and the oxygen saturation maintained at 5-10% by impeller agitation. The cultures are harvested before the end of the exponential growth phase, or after approximately 36 hours of incubation.

"Example 5" consists of verifying the protective potency of the antigen by employing it in a standard Kendrick test on mice.

"Example 6" involves analysis of the ACAP to ascertain its relative content of the respective amino acids of which it is composed. Sixteen different amino acids had measurable residues after hydrolysis and dessication. Proline and glutamic acid had relative amino acid values of 60 and 62, respectively.

"Example 7" involves use of the ACAP antigen in aqueous solutions to form pertussis vaccine or, in combination with diphtheria and tetanus antitoxins, to form composite DTaP vaccines.

The '052 patent has only two claims. Claim 1 reads as follows:

A purified *Bordetella* pertussis antigen characterized by the following features:

a relative molecular weight of between 67,000 to 73,000 as determined by 12% (w/w) polyacrylamide gel

electrophoresis;

a ratio of proline to glutamic acid of substantially 1:1 as determined by amino acid analysis.

Claim 2 is identical to Claim 1 except that it specifies "a relative molecular weight of 69,000."

The '120 patent contains only one claim, which is identical to Claim 1 of the '052 patent except that it specifies "a relative molecular weight of between 67,000 and 69,000."

The '080 patent contains fourteen composition claims (Nos.1-14) directed to a vaccine incorporating the antigen of the '052 and '120 patents and fourteen method claims (Nos.15-28) directed to inducing an immune response in a patient by administering the vaccine of Claims 1-14.

Claim 1, the only independent composition claim of the '080 patent, reads as follows:

A vaccine which comprises a proteinaceous material, which is derived from the outer membrane of *Bordetella* pertussis and is characterized by a relative molecular weight of about 67,000 to about 73,000 as determined by 12% (w/w) polyacrylamide gel electrophoresis and a proline:glutamic acid ratio of about 1:1 as determined by amino acid analysis in a pharmaceutically acceptable carrier or adjuvant.

Claim 15, the only independent method claim, reads as follows:

A method of inducing an immune response in a patient, which method comprises administering to said patient a vaccine which comprises a proteinaceous material, which is derived from the outer membrane of *Bordetella* pertussis and is characterized by a relative molecular weight of about 67,000 to about 73,000 as determined by 12% (w/w) polyacrylamide gel electrophoresis and a proline:glutamic acid ratio of about 1:1, as determined by amino acid analysis in a pharmaceutically acceptable carrier or adjuvant.

Prosecution history of the patents in suit

The U.K. application from which priority is claimed for the patents in suit was filed May 12, 1984. Its disclosure differed somewhat from that of the parent U.S. application. It began by acknowledging that acellular pertussis vaccines containing antigens extracted from the outer membrane of *B*. pertussis bacteria were known in the prior art, but asserted that "[w]e have now discovered that adenylate cyclase, an enzyme found in the cultures of *B*. pertussis .... is a major protective antigen against *B*. pertussis," a discovery which "permits the preparation of vaccine formulations comprising antigenic preparations which are free from, or contain reduced amounts of, other *B*. pertussis components which are responsible for the toxic side-effects demonstrated by whole-cell vaccines." The U.K. specification thus proceeded to describe a procedure for preparing "an antigenic preparation comprising adenylate cyclase .... [which] generally has a molecular weight of about 69,000 and an isoelectric point of 7.6-7.2 under preparative conditions.... [and which] may, if desired, contain minor quantities of other antigenic compounds .... [but is] preferably substantially free from other antigenic components."

It is therefore clear that at the time the U.K. priority application was filed, Novotny and his associates believed that the antigenic enzyme critical to effective protection against *B*. pertussis infection was adenylate cyclase, and they accordingly described a method of extracting it, along with other proteinaceous material, from the outer membrane of *B*. pertussis bacteria and purifying it to substantially eliminate the other

proteinaceous material. Indeed, Novotny admitted this in an Addendum to his 1995 paper "Identification of 68, 69 and 71 kDa Proteins of *Bordetella* Species," and added that it was not until after a visit by Professor Erik Hewlett and Dr. Alison Weiss from the United States in October 1984 that he "started to have serious doubt" that the protective enzyme was adenylate cyclase. (Exh. 22, Addendum.) He ultimately concluded that the effective 69 kDa antigen was *not* adenylate cyclase, but a different enzyme with "adenylate cyclase activity."(*See* Novotny Dep., June 4, 1997, Exh. 50 at 7, 43-44.)

Novotny's original U.S. application, filed May 1, 1985, accordingly described the key antigen less specifically as "proteinaceous material associated with adenylate cyclase activity (abbreviated to 'ACAP' hereinafter)" and added that it "may comprise the adenylate cyclase enzyme *per se* or a binding protein for the enzyme."

Claim 1 of the U.S. application as filed described the antigen merely as "proteinaceous material associated with adenylate cyclase activity (ACAP)." A series of dependent claims respectively added other characteristics of the material, such as "a relative molecular weight (MW) of 67,000-73,000," "an isoelectric point (pI) of 7.0-7.4 under preparative isoelectric focusing (IEF) conditions" and a "ratio of proline to glutamic acid residues ... [of] substantially 1:1."

All of the claims were rejected by the PTO Examiner as anticipated by or obvious in view of a paper by Erik Hewlett and J. Wolff entitled "Soluble Adenylate Cyclase from the Culture Medium of *Bordetella* pertussis*:* Purification and Characterization," published in the August 1976 edition of BACTERIOLOGY (the "Hewlett & Wolff article," Gram Aff., Exh. F). That article disclosed the extraction of adenylate cyclase from *B*. pertussis and its purification first by DEAE-cellulose chromatography and then by SDS electrophoresis. The purified product had a molecular weight of 69,000. Through some seven years of prosecution, and a series of continuation and divisional applications, the broadest claims were amended to import limitations from the original dependent claims, including those specifying molecular weight and the proline:glutamic acid ratio. Novotny then sought to overcome the rejection based on the Hewlett & Wolff article by filing a declaration under 37 CFR s. 1.132 of Erik Hewlett, one of the authors of the article, stating that the adenylate cyclase produced by the process described therein did not have a proline:glutamic acid ratio of substantially 1:1, as called for in the amended claims.

The PTO Examiner also repeatedly rejected all of the claims as anticipated by or obvious in view of the prior U.S. patent No. 3,141,824 to Robert Dahlstrom which was issued July 21, 1964 on an application filed May 29, 1961 (the "Dahlstrom patent," Exh. 6). Dahlstrom disclosed the extraction of a *B*. pertussis antigen from *B*. pertussis bacteria by a process which the Examiner concluded would produce some ACAP even if Dahlstrom had not specifically been seeking it.

After the rejection of the claims had been made final, the Examiner suggested that the rejection could be overcome if the claims were further amended to limit them to "A *purified* ... antigen." Such an amendment was filed August 22, 1992 (*see* Exh. 43) and ultimately resulted in the allowance of the applications.

Defendants' accused antigens and vaccine

Takeda has manufactured and sold an acellular pertussis vaccine in Japan since 1981. On September 12, 1980, it filed an application for a Japanese patent on the method of producing toxoid (antigen) for such a vaccine, and filed a corresponding U.S. application on January 30, 1981. U.S. patent No. 4,455,297 (the "Takeda patent") was issued June 19, 1984 on a continuation of the U.S. application. (*See* Exh. 5.)

Like Novotny, Takeda extracts a mixture of antigens from *B*. pertussis bacteria and treats the extract with formalin (an aqueous solution of formaldehyde) to remove toxins. Unlike Novotny, however, Takeda does not attempt to purify the mixture to eliminate other antigens and achieve a concentrated pertactin. Thus, pertactin constitutes only about 4% of the Takeda mixture of antigens. The relative molecular weight of the Takeda pertactin is approximately 69 kDa, but its proline:glutamic acid ratio is about 0.86:1, as measured by amino acid analysis. Further, Takeda's tests show that Takeda's pertactin has no adenylate cyclase activity, a finding which plaintiffs have not disputed.

DISCUSSION

I. *DEFENDANTS' MOTION FOR A MARKMAN RULING*

[1] Markman v. Westview Instruments, 517 U.S. 370, 116 S.Ct. 1384, 134 L.Ed.2d 577 (1996), holds that patent claim construction is an issue of law to be resolved by the Court. In jury cases, once the Court has construed the claims, the jury determines as an issue of fact whether the claims, as thus construed, are infringed-either literally or under the doctrine of equivalents-by the accused product or method. Wright Med. Tech., Inc. v. Osteonics Corp., 122 F.3d 1440, 1443 (Fed.Cir.1997).

[2] In determining the meaning of the claims, the Court must first examine the "intrinsic" evidence- *i.e.,* the claims themselves, the specification and, if in evidence, the prosecution history. Vitronics Corp. v. Conceptronic, Inc., 90 F.3d 1576, 1582 (Fed.Cir.1996). If this intrinsic evidence permits an unambiguous construction of the claim language, the Court need not, and indeed should not, consider extrinsic evidence, such as testimony from expert witnesses as to special meanings which the terms of the claims have for those skilled in the art. *See* id. at 1585.

In this case, defendants raise three questions concerning the applicability of the language of the broadest patent claims to their accused antigens. They contend (1) that their accused ACEL-IMUNE(R) vaccine does not include "purified" 69k, as called for in the claims of the '052 and '120 patents, but a mixture of antigens of which 69k constitutes only 4%; (2) that their 69k antigen does not have a proline:glutamic acid ratio of "substantially 1:1" as called for in the claims of the '052 and '120 patents, or "about 1:1" as called for in the claims of the '080 patent, but a ratio of 0.86:1; and (3) that the claims of all three patents in suit must be limited to cover only antigens having adenylate cyclase activity, which their antigens do not have. Thus the *Markman* issues to be resolved by the Court concern the meaning of the terms "purified" and "substantially 1:1" or "about 1:1," and whether a requirement of adenylate cyclase activity should be read into the claims. These issues will be discussed separately in that order.

A. *What does "purified" mean in the context of the patents in suit?*

[3] There can be no question as to the critical importance of this limitation which appears in each of the claims of the '052 and '120 patents. All the application claims were repeatedly rejected as unpatentable over the prior art references (especially the Dahlstrom patent) over some seven years of prosecution and through many continuation and divisional applications until, in response to the Examiner's repeated suggestion, the claims were finally amended to limit them to a "purified" 69k antigen. However, the parties hotly dispute the meaning of this limitation.

Plaintiffs contend that it means only that the desired material has been at least partially separated or isolated from an unwanted material-in other words, that *any* degree of purification suffices. Defendants urge a

construction at the opposite end of the spectrum, one requiring that the extracted proteinaceous material be put through all of the purification steps described in the specification, including the final immunopurification step of "Example 3." On the basis of the intrinsic evidence alone, it is difficult to conclude that either of these extreme positions is the correct one, although that of defendants seems closer to the mark.

Our analysis begins of course with the patent specification, which discloses a vaccine wherein the only active ingredient mentioned is "an antigenic preparation derived from *B*. pertussis comprising ACAP, optionally toxoided e.g. using formalin, glutaraldehyde or s-propiolactone, together with a pharmaceutically acceptable carrier therefor." ('052, 2/54-59.) All the specific examples of vaccine formulations given include "antigen according to the invention" as the only active ingredient. ('052, 9/36-10/26.)

The specification, after discussing the prior research in "isolating and purifying the 20 or more surface antigens of the *B*. pertussis organism and characterising their ability to induce immune reactions," states that among the antigens suggested for such investigation is adenylate cyclase. ('052, 1/54-64.) The specification then discusses several prior methods of reducing the toxicity of the extracted proteinaceous material, including that of defendant Takeda's U.K. Patent Specification2 047 358 A, which discloses production of a *B*. pertussis extract vaccine "involving removal of endotoxin from culture supernatants." ('052, 2/6-9.)

The specification initiates its discussion of the patented invention by stating:

It has now been discovered that certain proteinaceous material, associated with adenylate cyclase activity, as hereinafter described, found in the cultures of *B*. pertussis, is capable of providing protection against challenge by *B*. pertussis when administered to experimental animals. This discovery that the proteinaceous material usually associated with adenylate cyclase activity is a major protective antigen against *B*. pertussis permits the preparation of vaccine formulations comprising antigenic preparations *which are free from, or contain reduced amounts of, other known B*. pertussis *components* which may be responsible for the toxic side-effects demonstrated by whole cell vaccines.

('052 2/28-40; emphasis added.) The specification later adds that although the patented antigenic preparations may have " *minor quantities* of other antigenic compounds, in addition to the ACAP," they are "preferably *substantially free* from other antigenic compounds." ('052, 3/34-42; emphasis added.) Then, after describing the disadvantages of prior methods of extracting ACAP from the outer membrane of *B*. pertussis organisms, the specification states:

We have now discovered that ... extraction of *B*. pertussis organisms using regulated, mildly acidic conditions results in the extraction of substantially increased yields (about 40x better than previously reported techniques) of adenylate cyclase from the outer membrane in a form which is water-soluble.

('052, 4/6-12.) The specification then more specifically describes the extraction process, including incubation of the *B*. pertussis cells with an amino acid buffer and centrifuging to separate the cells from the ACAP-containing supernatant. ('052, 4/13-37.) It continues to describe use of the supernatant extract in the Kendrick test on mice, from which it was learned that

... [c]ontrol vaccines containing no adenylate cyclase activity were found to provide little or no protection against challenge with *B*. pertussis, suggesting that *ACAP may, in fact, be the most important factor in immunity*. Analysis of batches of non-protective whole-cell vaccine has also shown that non-protection tends to be associated with a lack of adenylate cyclase activity, further suggesting that *ACAP may be the key*

antigen necessary for eliciting an immune response against B. pertussis.

('052, 4/41-50; emphasis added.)

The specification then teaches a multi-step purification process for producing the "purified" ACAP antigen, commencing with the "Crude Outer Membrane Proteins" extracted in the first step, which is described in "Example 1." ('052, 5/54-55.) Plaintiffs have admitted that this "crude" mixture is not a "purified" material. (Exh. 30, Interrog.# 9.)

In support of their contention that the ACAP is "purified" only after it has been put through all the steps of the purification process described in the specification, including the immuno-purification step of "Example 3," defendants point out that "Example 3" is entitled "Purification of ACAP Using a Monoclonal Immunosorbent Column," ('052, 7/26-28), and that none of the products of the earlier steps in the process is described as a "purified" material. On the other hand, plaintiffs lay principal stress on the fact that in its initial, summary description of the purification process, the specification states:

The supernatant extract [from "Example 1"] ... may ... contain the ACAP in small quantities complexed with other proteins including fragments of LPS [lipopolysaccharide, which is suspected as the cause of toxic side effects], in which case it may be desirable to *purify further* the material for use in the vaccine formulations according to the invention. Thus, for example, *further purification* may be effected by ion exchange chromatography and/or by preparative isoelectro-focussing to eliminate complexed material....After the above-described *purification* steps the ACAP may, if desired, be *further purified,* for example by passing the material through an immunosorbent column containing an appropriate monoclonal antibody against the ACAP.

('052, 4/51-68; emphasis added.) Since the process steps denominated "Example 2(a)" and "Example 2(b)" are referred to as "purification" of the extract, plaintiffs argue that the product of those steps must be deemed to have been "purified" in the lexicography of the patent. However, this argument proves too much: because these steps are described as " *further* purification," carrying plaintiffs' argument to its logical conclusion would mean that the crude extract resulting from "Example 1" would likewise have to be deemed "purified." But, as already noted, plaintiffs have admitted that that product is *not* purified, as indeed they must in view of the prior art and the prosecution history of the applications for the '052 and '120 patents.

The limitation of the broadest claims of those applications to a "purified" ACAP material was added during prosecution to overcome the rejection of the claims as unpatentable over the cited references, particularly the Dahlstrom patent. Dahlstrom discloses the preparation of a *B.* pertussis antigen by extraction of proteinaceous material from *B.* pertussis cells in a saline solution (pH 8.5-10.5), which is later neutralized by the addition of sterile acid and centrifuged to separate the cells. The extracted antigen was tested for immunogenic potency by injection into mice and challenge by *B.* pertussis organisms introduced intracerebrally. Because Dahlstrom's antigen provided excellent immunity, with a 100% survival rate at a dosage of 0.015ml, it must have included a significant amount of ACAP, if we are to believe the teaching of the patents in suit that "vaccines containing no adenylate cyclase activity were found to provide little or no protection against challenge with *B.* pertussis " and that ACAP "may be the key antigen necessary for eliciting an immune response against *B.* pertussis." ('052, 4/41-50.) Thus there was ample support for the PTO Examiner's conclusion that the Dahlstrom process "[i]nherently ... would result in the extraction of Applicant's claimed protein. Note that Applicant's claims 28-32 do not require the antigen to be purified." (Exh. 41 para. 5.) Novotny acquiesced in that conclusion by amending all of the claims of the application

for the '052 patent so that they cover only a "purified" 69k antigen.

Nevertheless, in his co-pending application for the '120 patent, Novotny made another effort to obtain the coverage which he had thus relinquished, asserting claims similar to those of the '052 patent except that the word "purified" was replaced with the word "acellular" (*See* Exh. 31 at 3.) These broader claims were rejected as unpatentable over an article by Novotny and K. Cownley-"Effect of Growth Conditions on the Composition and Stability of the Outer Membrane of *Bordetella* pertussis "-published in 1978 as part of the Proceedings of the Third International Symposium on Pertussis (the "Novotny & Cownley article"). In rejecting the claims, the Examiner stated that "[t]he rejected claims do not contain any limitations which would distinguish the claimed products from the isolated outer membrane of the [Novotny & Cownley] article on the basis of purity." (Exh. 32 para. 6.) Novotny thereafter amended all the claims to limit them to "purified" 69k. (*See* Exh. 34.)

Therefore, there can be no dispute that the claim limitation to a "purified" material requires, at the least, sufficient purification to distinguish it from the extracted ACAP-containing material of the prior art, including the Dahlstrom patent and the Novotny & Cownley article, which was cited in rejecting the claims. It is clear that a "purified" ACAP is one that results from subjecting the mixture of proteins extracted from the outer membrane of *B*. pertussis bacteria to one or more purification steps which, to a substantial degree, isolate ACAP and eliminate the other antigens in the mixture. The only remaining question is *how much* purification is required for the material to be deemed "purified" within the meaning of the claims?

Defendants' argument that the third step (immunopurification), "Example 3," is necessary to achieve a "purified" material runs contrary to the specification's statement that the final step is optional:

After the above-described purification steps ["Example 2(a)" and "Example 2(b)"] the ACAP *may, if desired,* be further purifiedby passing the material through an immunosorbent column containing an appropriated monoclonal antibody against the ACAP ["Example 3"].

('052, 4/64-68; emphasis added.)

In opposition, plaintiffs argue that, because the limitation to a "purified" 69k was added to the broadest claims of the '052 and '120 patents to overcome their rejection as anticipated by or obvious in view of the prior Dahlstrom patent, the limitation should be construed as narrowing the claims only to the minimum extent necessary to overcome the rejection based on Dahlstrom. At the oral argument of the motions, plaintiffs' counsel conceded that the extraction and centrifugation steps of Dahlstrom constitute "purification." (Transcript of May 26, 1998 Oral Argument at 27.) Yet he argued that the claims of the '052 and '120 patents must be construed so as to cover antigens which have undergone *any* degree of purification beyond that performed by Dahlstrom.

However, that argument considers only one type of intrinsic evidence-the prosecution history-and ignores the equally important intrinsic evidence of the specification itself, which contains strong indications as to the meaning of the term "purified." The specification teaches that ACAP may be the "key antigen" for immunization against *B*. pertussis, that "the vaccine formulations according to the invention may, if desired, contain *minor* quantities of other antigenic compounds, in addition to the ACAP .... [but are] ... *preferably substantially free from other antigenic components*." ('052, 3/33-42; emphasis added.)

Moreover, the *only* antigen that is described in the specification as "purified" is the product of the

immunopurification step of "Example 3." At the oral argument, plaintiffs' counsel contended, with impressive ingenuity, that this step is unnecessary to produce a safe and effective antigen and was disclosed only so that Novotny "could characterize and identify [69k] as part of his teaching." (Tr. at 26-27.) But Novotny's specification taught immunopurification as the final step in producing an "antigen according to the invention." There is not the slightest suggestion that it was disclosed only as a means of identifying the new antigen which Novotny claims to have discovered.

After thorough consideration of all the intrinsic evidence, the Court concludes that the term "purified" in the claims of the '052 and '120 patents means that the mixture of proteins extracted from the outer membrane of *B*. pertussis has been treated to reduce the concentration of antigens other than 69k *at least* to the point where they are "minor" ingredients and 69k is the major remaining antigen. In other words, 69k must constitute, *at the minimum,* more than half of the extracted proteinaceous material present in the mixture.

If there were any doubt about this conclusion, resort to the most persuasive extrinsic evidence-the testimony of the patentee Novotny against his own interest-would only narrow the definition further in favor of the defendants. In pretrial depositions, Novotny stated unequivocally that the extracted material is not "purified" even after it has been subjected to the preliminary purification steps of "Example 2(a)" and "Example 2(b)" and not until it has gone through the final immunopurification step of "Example 3":

Q: At the end of Example 2(a), after you have performed that procedure, do you have something that is purified, as you understand the meaning of that term?

A: No, it was crude separation of some components which we weren't interested in, and some components which we wanted to proceed further, which was made, at that time, electrofocusing.

Q: What about the procedure of Example 2(b), which is: "Preparative flat bed isoelectrofocusing [in] granulated gel" .... At the end of that procedure, do you have something that was purified, as you understand that term?

A: No, it was still complex.

Q: Turning to Example 3 in column 7, that example is entitled: "Purification of ACAP using a monoclonal immunosorbent column."

A: That's correct.

Q: What were you trying to achieve in that procedure?

A: No, that's the final step of the purification which started in column 5, because [the] immunosorbent column was specific for the protein. So, it stuck to the column and was then eluted from the immunosorbent and you obtained a variety of a very pure preparation.

Q: So, according to your understanding, it is only after someone completes the procedure of Example 3, with monoclonal antibodies, that you have a purified substance, as you understand that term?

A: Yes.

Q: Turning back then to column 10, where you see the claim, am I right that you understand the term, "a purified *Bordetella* pertussis antigen," that refers to the product that you get after you complete Example 3?

A: Yes, sir. You have to finish all of it.

(Novotny Dep., June 2, 1997, Exh. 49 at 65-67.) It would be difficult to envision a clearer and more positive statement from the patentee himself that the position advanced by defendants as to the meaning of the term "purified" in the claims of his patents is absolutely correct, and that the construction for which plaintiffs contend is plainly wrong.

In light of this testimony, it is not surprising that plaintiffs urge the Court of follow the rule that where the intrinsic evidence permits an unambiguous construction of the meaning of the claim terms, reliance on extrinsic evidence is improper. However, plaintiffs themselves invite the Court to violate the rule by offering the declaration of Dr. Carine Capiau, an employee of plaintiff SmithKline, as to the meaning of the claims. She states: "In my opinion, the term 'purified' as used in the claims of the '052 patent and the '120 patent means that the desired material has been at least partially separated or isolated from an unwanted material." However, that opinion is pure *ipse dixit;* Capiau's declaration cites absolutely no evidence, intrinsic or extrinsic, in support of her opinion. She merely adds: "It is my further opinion that those skilled in the art would define 'purified' in such a manner." Such conclusory statements by an employee of one of the parties carry little if any probative weight, especially when they contradict clear and positive statements against interest by the patentee himself.

Thus, the best and most reliable extrinsic evidence strongly supports the Court's conclusion that the word "purified" in the claims of the '052 and '120 patents means that the proteinaceous material extracted from the outer membrane of *B*. pertussis bacteria must be purified *at least* to the extent that 69k is its major antigenic component. Indeed, if the intrinsic evidence left any doubt as to the meaning of the term "purified," resort to the patentee's own testimony would lead only to a further narrowing of the claim coverage to require completion of the entire purification process disclosed, including immunopurification in a chromatographic column charged with a monoclonal antibody which selectively binds 69k.

B. *Should the claims of* the '080 patent ***be construed to require "purified" 69k?***

Defendants contend that, although the limitation to a "purified" material does not appear in any of the claims of the '080 patent, those claims should be construed as if that limitation were present. That contention is based upon several undisputed facts. First, defendants point out that, in response to an interrogatory reading, "Do plaintiffs contend that the 'proteinaceous material' of Claim 1 of the '080 patent contains something other than the claimed antigen of Claim 1 of the '052 patent," plaintiffs answered, "No." (Exh. 30, Interrog.# 18.) Thus plaintiffs have admitted that the claims of the '080 patent cover only the "purified" material called for in Claim 1 of the '052 patent.

Second, defendants point out that all of the original claims of the application for the '080 patent specifically required a "purified" antigen and, during the prosecution of that application, Novotny repeatedly described the claimed antigen as "purified." For example, in an amendment filed April 7, 1995, he stated: "The present invention is concerned with use of a *purified B*. pertussis antigen for inducing an immune response." (Exh. 34 at 3; emphasis added.) However, two months later, on June 19, 1995, when Novotny substituted new claims which did not contain the "purified" limitation, he made no mention of that omission. (*See* Exh. 35 at 7.) The Examiner likewise never expressly noted the omission, perhaps because the applicant continued to

emphasize that the application covered " *one purified protein,* 69 kD antigen." (Decl. of Peter J. Cozens, Exh. 36 para. 5; emphasis added.)

One fact on which defendants do not rely in arguing for construction of the '080 patent to require a "purified" antigen, but which strongly argues for such a construction, is that the specification of the '080 patent is identical to that of the '052 and '120 patents, and contains all the teachings previously discussed. These include the statements that ACAP may be "the most important factor in immunity" and "the key antigen necessary for eliciting an immune response," and that although "vaccine formulations according to the invention may, if desired, contain *minor* quantities of other antigenic compounds, in addition to the ACAP," they are "preferably *substantially free* from other antigenic components." Moreover, as previously noted, in all of the illustrative formulations disclosed in the specification, ACAP is the only antigenic component listed.

An even more persuasive fact, likewise not relied on by defendants in support of this aspect of their motion, is that if the claims of the '080 patent are not construed as being limited to "purified" proteinaceous material, their patentability over the prior art cited against the application for that patent, including the Dahlstrom patent and the Novotny & Cownley article, would be in serious question. Before the "purified" limitation was added to the claims of the applications for the '052 and '120 patents, those claims differed from those of the '080 patent only in that the latter claims are directed to a vaccine formed by incorporating the antigen of the '052 and '120 patents in "a pharmaceutically acceptable carrier or adjuvant." Such use of the antigen is clearly not patentable over the disclosure of the '052 and '120 patents, which taught that precise use as the end purpose of the antigen. Thus the claims of the application for the '080 patent were rejected by the PTO Examiner for obviousness-type double patenting over the '052 and '120 patents, until Novotny overcame that rejection by pointing out that the application for the '080 patent was a division of the same parent application on which the '052 and '120 patents were based. (*See* Exh. 37 at 16.) As previously noted, the claims of the applications for the '052 and '120 patents were rejected as anticipated by or obvious in view of the cited art, a rejection in which Novotny acquiesced by amending the claims to limit them to a "purified" antigen. It therefore appears clear that if the claims of the '080 patent were not similarly limited, they would be equally vulnerable to invalidation as unpatentable over that same art.

[4] It is a well-established rule of claim construction that claims should be interpreted, if possible, so as to preserve their validity. *See* Amhil Enters. Ltd. v. Wawa, Inc., 81 F.3d 1554, 1561 (Fed.Cir.1996). In this case, that rule impels the Court strongly toward a limiting interpretation of the claims of the '080 patent. Notably, in their memorandum in opposition to defendants' motion for a *Markman* ruling, plaintiffs make no response whatsoever to defendants' argument for construction of the claims of the '080 patent to require a "purified" proteinaceous material. Perhaps this is because they recognize that, for the reasons discussed above, such a construction is necessary to preserve the validity of the claims.

Considering all of these factors, the Court concludes that the claims of the '080 patent must be construed to limit them, like those of the other two patents in suit, to a vaccine in which the extracted proteinaceous material is purified *at least* to the extent that 69k constitutes its major antigenic component.

C. *What is the meaning of "substantially 1:1" and "about 1:1" in the context of the patents in suit?*

[5] Each of the claims of the '052 and '120 patents calls for an antigen in which the ratio of proline to glutamic acid is "substantially 1:1," while each of the claims of the '080 patent describes that ratio as "about 1:1." There can be no dispute as to the importance of this limitation in the claims, for it was added to the

broadest claims during prosecution to overcome their rejection as unpatentable over the Hewlett & Wolff article, and the amended claims were allowed only after the filing of Hewlett's declaration attesting that the adenylate cyclase disclosed in the article did not have a proline:glutamic acid ratio of "substantially 1:1."

Both parties apparently agree that the terms "substantially" and "about" have the same meaning in the context of the patents in suit but, as might be expected, they differ considerably as to what that meaning is. Plaintiffs argue that "[t]hese are not terms which would have a unique meaning in the art to which the patent relates" and that they merely "indicate that the ratio of proline to glutamic acid explicitly does not have to be *exactly* 1:1." (Pls.' Mem. in Opp. to Non-infringement/ *Markman* Mot. at 17.) Plaintiffs accordingly argue that it should be left for the jury to decide whether the 0.86:1 ratio of defendants' products is "substantially" or "about" 1:1.

Defendants urge the Court to interpret the terms in light of both intrinsic and extrinsic evidence. First, defendants point out that the only guide in the specification to the meaning of the terms is found in "Example 6," which involves amino acid analysis of ACAP. This analysis found proline and glutamic acid (including glutamine) residues of 60 and 62 respectively-a ratio of 0.97:1.

Defendants also rely upon the deposition of Dr. Erik Hewlett, whose declaration was submitted to the PTO to overcome a rejection of the claims as unpatentable over two articles co-authored by him. In that declaration, Dr. Hewlett stated that his tests of a 70kD portion of the adenylate cyclase toxin disclosed in the aforementioned Hewlett & Wolff article (curiously, not one of the two articles cited in the rejection) was subjected to amino acid analysis and found to have a proline:glutamic acid (+glutamine) ratio of 0.32:1. Thus plaintiffs have presented Dr. Hewlett as an expert in this branch of protein analysis. In his deposition, Dr. Hewlett expressed his understanding, as one skilled in the art, of the meaning of the term "substantially 1:1":

Q: ... At the time you were executing this declaration, I want to find out if you had some understanding in your mind what you as a person skilled in the art thought that claim meant?

A: Yes.

Q: Okay. And in particular what "substantially 1 to 1" meant to you.

A: I can tell you what it meant to me.

Q: Okay.

A: Because I was-

Q: Why don't you-

A. -making the interpretation. Substantially I interpreted as being the equivalent of statistically-not statistically significantly different than 1, which is essentially plus or minus 5 percent.

(Hewlett Dep., Aug. 13, 1997, Exh. 54 at 208-09.)

In their briefs, plaintiffs attempted to stretch this range to twice its width by interpreting it as contemplating

"5 percent plus or minus *per amino acid* " (emphasis added), so that it would encompass the entire span from 0.9:1 to 1.1:1. That is a creative approach, but is inappropriate in this context. It would be logically applicable if there were a potential error of plus or minus 5% in measuring the value of each of the two amino acids, so that one might be 5% too high and the other 5% too low, for a possible spread of 10%. However, the question put to Dr. Hewlett did not contemplate measurement tolerances, but merely asked what the expression "substantially 1:1" in the patent claims means to him as a person skilled in the art. His testimony is therefore subject to only one reasonable interpretation: that "substantially 1:1" means within plus or minus 5% of equality-that is, between 0.95:1 and 1.05:1.

Moreover, even if the Court were to accept plaintiffs' imaginative approach and construe "substantially 1:1" as covering any ratio between 0.90:1 and 1.1:1, it still would not encompass the proline:glutamic acid ratio of 0.86:1 in defendants' antigen. Realizing this, plaintiffs' counsel strained his ingenuity still further and, at oral argument, contended that the plus or minus 10% range should be measured from the "starting point" of the 0.97:1 ratio calculated from "Example 6" of the specification. This would extend the range all the way down to 0.87:1, which plaintiffs argue is so close to defendants' 0.86:1 ratio that a jury could find the difference "insubstantial." (Tr. at 42-45.) In his desperate advocacy, plaintiffs' able counsel ignored the fact that the patent claims specify a ratio of "substantially 1:1," not "substantially 0.97:1." Thus the "starting point" from which to measure whether there is "substantial" equality is clearly 1:1, not 0.97:1.

The only intrinsic evidence as the meaning of the terms "substantially 1:1" and "about 1:1" is the one example given in the specification, in which the ratio of the residue values of the two amino acids is 60:62 (or 0.97:1), which is to say that they are within 3% of one another. And the only extrinsic evidence as to such meaning which has been presented to the Court is the testimony of plaintiffs' own expert that the terms mean to him, as a person skilled in the art, that the residue values of the two amino acids are within 5% of each other.

Faced with such evidence, plaintiffs understandably urge the Court to make no *Markman* ruling as to the meaning of the terms in question and leave this determination for the jury. However, the Court believes that course of action would be an abdication of the responsibility which *Markman* places on the Court. The jury is not likely to have any better evidence as to the meaning of the terms than is now available to the Court. At the trial, each side would surely present its own partisan expert to testify as to what the claims mean to those skilled in the art, and surely the plaintiffs' expert would assign to the terms a range of ratios broad enough to include the 0.86:1 proline:glutamic acid ratio in defendants' antigen, while defendants' equally eminent expert would narrow the range to exclude defendants' antigen. With those contradictory opinions offsetting one another, the issue would have to be determined on the basis of the evidence now available: the intrinsic evidence of the example given in the specification ((plus-or-minus sign)3%) and the extrinsic evidence of the testimony against interest of defendants' expert ((plus-or-minus sign)5%).

In light of such evidence, the Court concludes that the terms "substantially 1:1" and "about 1:1" mean that the proline and glutamic acid values are within 5% of each other-that is, the ratio between these values must fall within the range of 0.95:1 to 1.05:1. There is no evidence in the record, intrinsic or extrinsic, which would support any broader reading of the language.

D. *Should the claims be construed to require "adenylate cyclase activity"?*

[6] All of the claims of the '052 and '120 patents are directed to "A purified *Bordetella* pertussis *antigen,*" while all of the claims of the '080 patent call for "a vaccine which comprises a *proteinaceous material*."

Defendants contend that even though none of the claims specifically requires adenylate cyclase activity, the terms "antigen" and "proteinaceous material" should be construed, in light of the specification, as limited to a material having adenylate cyclase activity. Defendants base this contention principally upon the specification's statement that:

... Control vaccines containing no adenylate cyclase activity were found to provide little or no protection against challenge with B. pertussis, suggesting that ACAP may, in fact, be the most important factor in immunity.

('080, 4/18-21; emphasis added.) Defendants further point out that in all of the illustrative vaccines disclosed in the specification, "antigen according to the invention" is the only immunogenic material listed. Thus, they reason, the patents teach that the claimed "antigen" or "proteinaceous material" must have adenylate cyclase activity.FN8

FN8. "Adenylate cyclase activity" is the enzymatic activity of adenylate cyclase, which is measured, *e.g.*, by the rate of the conversion of ATP (adenosine 5'-triphosphate) to cAMP (cyclic adenosine 3',5'-monophosphate).

In opposition, plaintiffs point out that the specification refers to:

... This discovery that proteinaceous material *usually* associated with adenylate cyclase activity is a major protective antigen against *B.* pertussis....

('052, 2/33-35; emphasis added.) Plaintiffs argue that the use of the word "usually" means that the claimed antigen need not have adenylate cyclase activity. However, the force of this argument is somewhat weakened by the fact that the sentence immediately preceding the one partially quoted by plaintiffs, which identifies what is referred to as "[t]his discovery," does not contain the word "usually":

It has now been discovered that certain proteinaceous material, associated with adenylate cyclase activity, as hereinafter described, found in the cultures of *B.* pertussis, is capable of providing protection against challenge by *B.* pertussis when administered to experimental animals.

('052, 2/28-33.) Moreover, immediately after stating that ACAP may be "the most important factor in immunity," the specification adds:

... Analysis of batches of non-protective whole-cell vaccine has also shown that non-protection tends to be associated with a lack of adenylate cyclase activity, *further suggesting that ACAP may be the key antigen necessary for eliciting an immune response against B.* pertussis.

('052, 4/45-50; emphasis added.) The use of the words "key" and "necessary" strongly suggests that adenylate cyclase activity is not a merely optional characteristic of the antigen.

Finally, as previously discussed, in the U.K. application on which plaintiffs' claim of priority is based, the patented antigen was not described as merely having adenylate cyclase *activity* but as being adenylate cyclase *per se*. Before the parent U.S. application was filed, Novotny had talked to others, including Dr. Hewlett, and concluded that the critical antigen might not be adenylate cyclase but could be either "the

adenylate cyclase enzyme *per se* or a binding protein for the enzyme." ('052, 2/48-49.)

Now plaintiffs seek to broaden the scope of their protection even further beyond the patentee's original concept and the teachings of his specification to cover antigens and vaccines that do not even have adenylate cyclase *activity*. The broader coverage they now seek not only is unsupported by the teaching of the specification, as required by 35 U.S.C. s. 112, but is flatly contradicted by that teaching.

In Genentech, Inc. v. Wellcome Found. Ltd., 29 F.3d 1555 (Fed.Cir.1994), the Court ruled that the terms of the patent claims, even though worded broadly enough to cover many permutations, should be construed to cover only those permutations which are enabled by the specification:

... As Dr. Goeddel testified, an infinite number or permutations of natural t-PA are covered by these other definitions. Many of these permutations would not be capable of binding to fibrin and would thus be inoperative. There is no basis provided in the specification for determining which of these permutations are operative and which are not.... Thus we are unwilling to say that the specification satisfies the enablement requirement of 35 U.S.C. s. 112 para. 1 (1988) with respect to these broader definitions, or that the PTO could have relied on these definitions in issuing the patent.... We conclude therefore that the phrase "human tissue plasminogen activator" appearing in the '075 and '330 claims means natural t-PA.

Id. at 1564-65 (internal citations omitted).

Here, the circumstances much more strongly favor a narrow reading of the claims, because the specification not only fails to teach the preparation of antigens having no adenylate cyclase activity, but affirmatively teaches that such antigens have little or no immunogenic efficacy. The very essence of the specification's message is that a protein having adenylate cyclase activity, or ACAP, may be "the key antigen necessary for eliciting an immune response against *B*. pertussis," and that vaccines without it "provide little or no protection against challenge with *B*. pertussis." The claims surely cannot validly be interpreted to cover materials which the specification expressly declares to be inoperative. There would be no *quid pro quo* for granting a patentee the right to exclude others from using something that his specification clearly instructs them *not* to use.

At the oral argument, plaintiffs' counsel attempted to downplay the importance of adenylate cyclase activity by making the startling assertion that none of the vaccines actually being produced and used has adenylate cyclase activity because all of it is destroyed in the purification process. (Tr. at 98.) He argued that Novotny's specification discusses adenylate cyclase activity not because it is needed in the vaccine, but only because it "is present at some stages so you know you're on the right path." (Tr. at 99.) He added that Novotny did not say "a single word ... that tells the worker to test for adenylate cyclase activity." (Tr. at 99-100.) Defendants' counsel immediately corrected the latter assertion by pointing out that the specification states: "Adenylate cyclase activity was assayed by the method of Hewlett, E., and Wolff, J. (J. BACTERIOL.(1976) 127, 890-898)." (*See* Tr. at 102-03 (citing '052, 2/50-52).)

Plaintiffs' argument is nothing more than a desperate attempt to disown the core teaching of Novotny's specification. Novotny taught not only that "[c]ontrol vaccines containing no adenylate cyclase activity were found to provide little or no protection against challenge with *B*. pertussis " and that "ACAP may be the key antigen necessary for eliciting an immune response against *B*. pertussis," but also that "ACAP may, in fact, be the most important factor in immunity" and that "non-protection tends to be associated with a lack of adenylate cyclase activity." ('052, 4/41-50.)

Moreover, nowhere in Novotny's specification is there the slightest suggestion that adenylate cyclase activity is destroyed in the purification process, or that it is unnecessary in the final vaccine. On the contrary, in its discussion of each successive step of purification, the specification expressly states that both the objective and the result of the step were to purify the ACAP (*i.e.,* adenylate cyclase activity protein) which had been extracted from the outer membrane of *B.* pertussis cells. For example, in describing the result of the first purification step, "Example 2(a)," the specification states: "The ACAP was present in the material unretarded by the column, as shown by SDS-PAGE, but was also present in the retarded material eluted by 0.2M NaCl." ('052, 6/37-40.) In describing the next purification step, "Example 2(b)," the specification states: "The ACAP was detectable as two bands, one of pI 7.0, and the other (diffuse) band of pI 7.2-7.4. Adenylate cyclase activity was associated almost entirely with the central band (pI 7.0) but monoclonal antibodies to ACAP bound both bands strongly." ('052, 7/3-7.) The final purification step, "Example 3," is entitled "Purification of ACAP Using a Monoclonal Immunosorbent Column," and the objective of this procedure is described as "[t]o separate the ACAP on the immunosorbent column ...." ('052, 7/57-58.)

In view of the undisputed fact that defendants' ACEL-IMMUNE(R) vaccine has no adenylate cyclase activity, it is understandable that plaintiffs would strain to rewrite Novotny's specification, but they cannot discard it altogether because its teaching was the sole consideration for the patent grant. If what plaintiffs now say about the irrelevance of adenylate cyclase activity is correct (as it apparently is), there was a total failure of consideration.

The Court therefore concludes that the terms "antigen" and "proteinaceous material" in the claims of the patents in suit must be interpreted to cover only antigens having adenylate cyclase activity.

II. *DEFENDANTS' MOTION FOR SUMMARY JUDGMENT OF NON-INFRINGEMENT*

[7] [8] As noted above, once the Court has construed the claims as a matter of law, it is a question of fact for the jury whether the claims, as so construed, are infringed by the accused product or method. Wright Med. Tech., Inc. v. Osteonics Corp., 122 F.3d 1440, 1443 (Fed.Cir.1997). In order for there to be infringement-either literally or under the doctrine of equivalents-"each and every limitation set forth in a patent claim must be found in the accused" product or method. CVI/Beta Ventures, Inc. v. Tura LP, 112 F.3d 1146, 1161 (Fed.Cir.1997). The patenteebears the burden of proving infringement by a preponderance of the evidence. *Id.*

[9] [10] [11] Literal infringement requires that the accused product or method contain each limitation of the claim exactly; any deviation from the claim precludes a finding of literal infringement. Litton Sys., Inc. v. Honeywell, Inc., 140 F.3d 1449, 1453-54 (Fed.Cir.1998). A product or method that does not literally infringe may nonetheless infringe under the doctrine of equivalents if every element in the claim is equivalently present in the accused product or method. *See* Warner-Jenkinson Co. v. Hilton Davis Chem. Co., 520 U.S. 17, ----, 117 S.Ct. 1040, 1054, 137 L.Ed.2d 146 (1997); Sage Prods., Inc. v. Devon Indus., Inc., 126 F.3d 1420, 1423 (Fed.Cir.1997). A claim is equivalently present if only "insubstantial differences" distinguish the missing claim element from the corresponding aspects of the accused device. *Id.; accord* Dawn Equip. Co. v. Kentucky Farms Inc., 140 F.3d 1009, 1015-16 (Fed.Cir.1998). The Supreme Court has cautioned that "[i]t is important to ensure that the application of the doctrine [of equivalents] ... is not allowed such broad play as to effectively eliminate [an] element in its entirety." Warner-Jenkinson, 117 S.Ct. at 1049; *see also* Litton, 140 F.3d 1449, 1454-55. Accordingly, "[a]lthough equivalence is a factual

matter normally reserved for a fact finder, the trial court should grant summary judgment in any case where no reasonable fact finder could find equivalence." Sage Prods., 126 F.3d at 1424; *see also* Warner-Jenkinson, 117 S.Ct. at 1053 n. 8 ("Where the evidence is such that no reasonable jury could determine two elements to be equivalent, district courts are obliged to grant partial or complete summary judgment.... Thus, under the particular facts of a case, ... if a theory of equivalence would entirely vitiate a particular claim element, partial or complete judgment should be rendered by the court, as there would be no further *material* issue for the jury to resolve.") (original emphasis).

Summary judgment is appropriate 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 a judgment as a matter of law." Fed.R.Civ.P. 56(c). A genuine issue for trial exists if, based on the record as a whole, a reasonable jury could find in favor of the non-moving party. Anderson v. Liberty Lobby, Inc., 477 U.S. 242, 248, 106 S.Ct. 2505, 91 L.Ed.2d 202 (1986). On a motion for summary judgment, all evidence must be viewed and all inferences drawn in the light most favorable to the non-moving party. Kader v. Paper Software, Inc., 111 F.3d 337, 338 (2d Cir.1997). The role of the court on a motion for summary judgment is not to decide issues of fact, but merely to determine whether there are issues of fact to be tried. Vann v. City of New York, 72 F.3d 1040, 1049 (2d Cir.1995). However, summary judgment "is properly regarded not as a disfavored procedural shortcut, but rather as an integral part of the Federal Rules as a whole, which are designed 'to secure the just, speedy, and inexpensive determination of every action.' " Celotex Corp. v. Catrett, 477 U.S. 317, 327, 106 S.Ct. 2548, 91 L.Ed.2d 265 (1986) (quoting Fed.R.Civ.P. 1).

The party seeking summary judgment bears the initial burden of "informing the district court of the basis for its motion" and identifying the matter "it believes demonstrate[s] the absence of a genuine issue of material fact." Celotex, 477 U.S. at 323, 106 S.Ct. 2548. Upon the movant's satisfaction of that burden, the onus then shifts to the non-moving party to "set forth specific facts showing that there is a genuine issue for trial." Liberty Lobby, 477 U.S. at 250, 106 S.Ct. 2505. At this stage, the non-moving party "must do more than simply show that there is some metaphysical doubt as to the material facts." Matsushita Elec. Indus. Co. v. Zenith Radio Corp., 475 U.S. 574, 586, 106 S.Ct. 1348, 89 L.Ed.2d 538 (1986). Bald assertions or conjecture unsupported by evidence are insufficient to defeat a motion for summary judgment. PDK Labs, Inc. v. Friedlander, 103 F.3d 1105, 1111 (2d Cir.1997).

[12] In this case, the record clearly establishes that there is no genuine issue of material fact with respect to the infringementof any of the patent claims as construed by the Court.

A. *The claim requirement of a "purified" antigen*

It is undisputed that, in defendants' accused pertussis antigen, the 69k enzyme constitutes only approximately 4% of its total composition. In preparation of the antigen, there is no effort to isolate 69k from the other antigens extracted from the outer membrane of the *B*. pertussis cells. Instead, the mix of antigens is merely treated to remove endotoxin, first by precipitation with a calcium phosphate gel and then by zonal centrifuging on a sucrose density gradient.FN9 Defendants assert that Takeda's production process has been essentially unchanged since production was begun in 1981, long before the filing of the U.K. application from which plaintiffs claim priority. Plaintiffs describe the calcium phosphate gel treatment which was added by Takeda in 1986 as a "purification" step, although they state that it was added merely to increase the amount of material that could be loaded onto the rotor of the centrifuge and thereby "essentially double" Takeda's production of acellular pertussis vaccine to meet the increased demand imposed by its

supply agreement with American Cyanamid. But, regardless of the name given to that step, it does not change the fact that the Takeda acellular pertussis vaccine is, and has been from the outset of production, a mixture of many antigens in which 69k constitutes only 4% of the total.

FN9. In zone-velocity centrifugation, particles are impelled to move through a sucrose solution of increasing concentration by centrifugation and are separated by virtue of their movement through the sucrose gradient at different speeds dependent upon their mass, density and shape. The fractions thus separated are removed seriatim at the center of the rotor by pumping high density sucrose into the outer edge of the rotor.

69k may be an important component of defendants' vaccine, but it is nonetheless only a minor component in terms of weight and volume. There is and has been no attempt to isolate 69k or produce an antigenic preparation which, in the words of the specification, is "free from or contain[s] reduced amounts of other known *B*. pertussis components...." Indeed, in the Takeda vaccine, the other antigens extracted with 69k from the outer membrane of the *B*. pertussis cells constitute 96% of the total composition. They clearly have not been removed to the extent that they represent only a "minor" part of the total.

There is no genuine issue of fact to be tried by the jury as to whether any of the claims of the '052 and '120 patents, as construed by the Court to require purification of the extracted proteinaceous material at least to the extent that 69K is the major ingredient (*i.e.,* constituting *at least* 50%) of the composition, have been literally infringed by defendants' ACEL-IMUNE(R) vaccine or by the pertussis antigen component thereof. Moreover, no reasonable jury could find that an antigen containing only 4% 69k is the "equivalent" of the "purified" 69k called for in those claims.

B. ***The claim requirement of a proline:glutamic acid ratio of "substantially" or "about" 1:1***

It is undisputed that the ratio of proline to glutamic acid in Takeda's accused 69k antigen is 0.86:1. The Court has construed all the claims of the patents in suit as requiring a proline:glutamic acid ratio within a *maximum* range from 0.95:1 to 1:1.05. There is therefore no genuine issue of fact to be tried by the jury as to whether the claims, as thus construed, are literally infringed by the pertussis antigen incorporated in defendants' accused ACEL-IMUNE(R) vaccine. However, because neither the specification nor the prosecution history discusses the significance of the ratio of proline to glutamic acid, the Court cannot conclude as a matter of law that no reasonable jury could find that the proline:glutamic acid ratio of defendants' ACEL-IMUNE(R))) is the equivalent of that called for in the claims.

C. ***The implied claim requirement of "adenylate cyclase activity"***

In support of their motion for summary judgment of non-infringement, defendants have submitted the declaration of Dr. Richard L. Friedman, Professor of Microbiology and Immunology at the University of Arizona College of Medicine and an eminent scientist in the field for over 20 years. He declared that he had tested the acellular pertussis vaccine incorporated in defendants' ACEL-IMUNE(R) and concluded that it "does not have adenylate cyclase enzymatic activity." He attached to his declaration a detailed protocol of his assay procedure and a report of his calculations. Plaintiffs have not disputed his findings nor submitted evidence of any kind to the contrary. Furthermore, plaintiffs' counsel conceded at the oral argument that defendants' ACEL-IMUNE(R))) has no adenylate cyclase activity. (Tr. at 14.)

Accordingly, the Court concludes, as a matter of law, that none of the claims in suit, as construed by the Court to require adenylate cyclase activity, is or has been literally infringed by defendants. Moreover,

because the specification of each of the patents teaches that adenylate cyclase activity is the "key" to effective immunization against pertussis, the Court further concludes that no reasonable jury could find that a vaccine without adenylate cyclase activity infringes any of the claims under the doctrine of equivalents.

For the reasons stated, defendants' motion for summary judgment of non-infringement is granted.

III. *MOTIONS FOR SUMMARY JUDGMENT OF INVALIDITY*

Although defendants' motion for summary judgment of non-infringement has been granted, the Court will consider defendants' motions for summary judgment of invalidity and plaintiffs' motion for partial summary judgment dismissing certain of the affirmative defenses of invalidity. *See* Phonometrics, Inc. v. Northern Telecom Inc., 133 F.3d 1459, 1468 (Fed.Cir.1998) (district court has discretion to consider validity of patent despite granting summary judgment of non-infringement); *see also* Cardinal Chem. Co. v. Morton Int'l, Inc., 508 U.S. 83, 99-100, 113 S.Ct. 1967, 124 L.Ed.2d 1 (1993) (discussing interest in finality of judgments in patent litigation and importance of resolving questions of patent validity). As discussed below, these motions concern the issues of best mode and anticipation.

A. *Invalidity based on Failure to Disclose the Best Mode*

Defendants move for summary judgment that the three patents in suit are invalid for failure to comply with the "best mode" requirement of 35 U.S.C. s. 112. In particular, defendants claim that at the time the parent U.S. application was filed, the patentee (Novotny) had a preferred method of practicing his invention (employing a specific monoclonal antibody known as BB05 in the final, immunopurification step described in "Example 3") yet failed to disclose that method in the application. Plaintiffs move for partial summary judgment that the 1990 deposit of a monoclonal secreting hybridoma satisfies the best mode requirement.

Section 112, which sets out the disclosure requirements for a patent application, provides in pertinent part:

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

35 U.S.C. s. 112, para. 1. This provision contains three basic requirements: written description; enablement; and best mode. At issue here is the best mode requirement, the "sole purpose" of which is to "restrain inventors from applying for patents while at the same time concealing from the public preferred embodiments of their invention which they have in fact conceived." Chemcast Corp. v. Arco Indus. Corp., 913 F.2d 923, 926 (Fed.Cir.1990) (quoting *In re Gay,* 50 C.C.P.A. 725, 309 F.2d 769, 772 (Cust.&Pat.App.1962)). In other words, "[t]he best mode requirement ... is intended to ensure that a patent applicant plays 'fair and square' with the patent system. It is a requirement that the *quid pro quo* of the patent grant be satisfied." Amgen, Inc. v. Chugai Pharmaceutical Co., 927 F.2d 1200, 1209-10 (Fed.Cir.1991).

[13] The determination as to whether the best mode requirement has been satisfied is a question of fact involving two components. Transco Prods. Inc. v. Performance Contracting Group, Inc., 38 F.3d 551, 559-60 (Fed.Cir.1994); Amgen, 927 F.2d at 1209. The first step involves determining whether, at the time the application was filed, the inventor knew of a mode of practicing the claimed invention that he considered to be better than any other. This inquiry into the necessity of disclosure is wholly subjective. Second, if the

inventor in fact contemplated such a preferred mode so that disclosure was required, it must be determined whether the disclosure was adequate to enable one skilled in the art to practice the best mode. This second step is a largely objective inquiry that depends upon the scope of the claimed invention and the level of skill in the art. *See* United States Gypsum Co. v. National Gypsum Co., 74 F.3d 1209, 1212 (Fed.Cir.1996); Transco, 38 F.3d at 560; Chemcast, 913 F.2d at 927-28.

[14] With respect to the second, objective inquiry, the Federal Circuit has emphasized that the disclosure does not have to enable "an exact duplication" of the best mode in order to be deemed adequate. Amgen, 927 F.2d at 1212 ("What is required is an adequate disclosure of the best mode, not a guarantee that every aspect of the specification be precisely and universally reproducible."). In addition, it is well-settled that an applicant need not have an intent to conceal in order to violate the best mode requirement: "A best mode violation may occur if the disclosure of the best mode is so objectively inadequate as to effectively conceal the best mode from the public." U.S. Gypsum, 74 F.3d at 1215.

[15] In sum, a holding of invalidity for failure to disclose the best mode requires clear and convincing evidence that the inventor both knew of and failed to disclose a better mode of carrying out the claimed invention than was set forth in the specification. Transco, 38 F.3d at 560. The burden of supplying such evidence is on the defendants. *See id*.

1. ***Inventor's Contemplation of Best Mode***

[16] The parties do not dispute that, at the time the U.S. application was filed, Dr. Novotny employed the specific monoclonal antibody identified as BB05 in his experiments with the purification process. Rather, the parties dispute whether at that time Novotny in fact viewed BB05 as the best mode of purifying the claimed antigen.

At best, the evidence cited by defendants-excerpts from depositions of Novotny and Ivanyi-reaffirms the undisputed fact that Novotny actually used BB05 in an immunoaffinity column and chose it over at least one other monoclonal antibody. It does not, however, conclusively establish that Novotny believed that the best mode of practicing his invention involved the use of BB05 as the monoclonal antibody in an immunosorbent column. Granted, it would seem logical to conclude that Novotny deemed BB05 to be the best available substance for practicing his invention, given that (1) he was using BB05 in the immunoaffinity column at the time the application was filed, (2) he appears to have chosen BB05 over other monoclonal antibodies, and (3) he seems to have been aware of no equally effective antibody. However, even though the conclusion that Novotny, at the time of filing, contemplated use of BB05 for immunopurification as the best mode of practicing the invention seems virtually inescapable, the lack of any direct evidence as to his state of mind makes it difficult for the Court to conclude that no reasonable jury could find otherwise. This subjective determination must therefore be left for a jury.

2. ***Adequacy of Disclosure***

Even assuming that Novotny contemplated a best mode involving BB05, plaintiffs argue that the best mode was adequately disclosed. Assessing this objective component requires consideration of the adequacy of (1) the reference in the U.S. parent application to a "monoclonal immunoglobulin specific for ACAP," and (2) the subsequent hybridoma deposit and the amendment of the application to refer to that deposit.

a. "*Monoclonal immunoglobulin specific for ACAP*"

[17] Plaintiffs contend that the original U.S. application itself satisfies the best mode requirement. Although the original application did not specifically refer to BB05 or explain how to prepare that antibody, its specification does disclose the following:

Mouse ascitic liquid containing a monoclonal immunoglobulin specific for ACAP was precipitated at room temperature by the addition of 2 volumes of 27% w/v Na_2SO_4 and left to stand for 2-4 hours before being sedimented (2000g for 15 min).

Citing a declaration by Novotny filed during prosecution of the '080 patent, plaintiffs assert that the phrase "a monoclonal immunoglobulin specific for ACAP" refers to BB05, the antibody actually used by Novotny. (*See* Novotny Decl. para. 15, Exh. 1 to Pls.' Reply Mem. in Supp. of Deposit & Foreign Priority Mot.) Even if this is true, however, the question remains whether this reference discloses BB05 sufficiently to enable one skilled in the art to prepare it.

Plaintiffs contend that the above-quoted language from the specification "discloses the use of a hybridoma producing an appropriate antibody to bind the claimed antigen, and by itself is sufficient to enable a person of skill in the art to practice the best mode of invention." (Pls.' Mem. in Opp. to Best Mode Mot. at 4.) Plaintiffs' argument begins with the premise that the best mode disclosure does not have to enable an "exact duplication" of the best mode. *See* Amgen, 927 F.2d at 1212 ("What is required is an adequate disclosure of the best mode, not a guarantee that every aspect of the specification be precisely and universally reproducible."). Thus, plaintiffs argue not that the original application enables the reproduction of BB05 itself, but that it does teach the use of an "adequate" antibody for purposes of immunopurification.

Plaintiffs rely on two principal items of evidence in support of their contention. First, plaintiffs cite a statement made by the PTO Examiner during prosecution of the '080 patent that "it is the position of the Examiner that making an antibody which recognizes ACAP is within ordinary skill." ('080 Examiner Statement at 7, June 11, 1996, Exh. 4 to Pls.' Mem. in Opp. to Best Mode Mot.) However, as defendants point out, the Examiner subsequently noted that if BB05 were shown to have properties or characteristics superior to other monoclonal antibodies which could also be defined as specific for ACAP, then best mode concerns might be raised. (*See* id.) Plaintiffs also cite the more specific declaration of their employee/expert, Dr. Carine Capiau, that the U.S. application discloses and enables "the equivalent of BB05." (Capiau Decl. para. 23, Exh. 3 to Pls.' Mem. in Opp. to Best Mode Mot.)

Defendants counter that the brief reference to "a monoclonal immunoglobulin specific for ACAP" is wholly insufficient to enable a person skilled in the art to reproduce BB05. They argue that "[n]othing [in the original specification] tells the reader how the inventor obtained the monoclonal immunoglobin 'specific for ACAP.' " (Defs.' Mem. in Opp. to Deposit Mot. at 4-5.) They point out that while Montaraz's work demonstrates that it is possible to produce more than one "monoclonal immunoglobulin specific for ACAP," the disclosure contains no reference to the superior properties of BB05 by which one skilled in the art could judge whether he or she had obtained a monoclonal antibody equivalent to BB05, as opposed to any other antibody. FN10

FN10. Defendants attempt to buttress their contention by noting that the U.K. High Court of Justice, Chancery Division, Patents Court and the European Patent Office Appeal Board held the U.K. patent invalid because, *inter alia,* the U.K. application-which contained an essentially identical disclosure with respect to the monoclonal immunoglobulin-failed to enable one skilled in the art to identify and reproduce BB05. Plaintiffs respond by pointing out that the law applied by those tribunals does not contain a "best

mode" requirement, and that the patent was invalidated for failure to enable.

Although the U.K. court discussed enablement and not best mode, the issue it addressed is nearly identical to that before this Court: whether the specification enables the reproduction of BB05. However, the U.K. court addressed this issue in the context of a specification that identified the key antigen as adenylate cyclase, not ACAP. It may be that the U.S. application's corrected reference to ACAP would make it easier to derive BB05 from that specification than from the U.K. specification. Moreover, the U.K. court ruled in its capacity as a finder of fact and with the benefit of trial testimony. And of course, this Court is not bound by the determinations of the U.K. court, for the best mode determination in the instant case must be made by reference to U.S. patent law, not the law of a foreign tribunal. *See* Medtronic, Inc. v. Daig Corp., 789 F.2d 903, 907-08 (Fed.Cir.1986); Cuno Inc. v. Pall Corp., 729 F.Supp. 234, 238-39 (E.D.N.Y.1989). Although defendants' arguments have weight, for summary judgment purposes the Court cannot ignore Dr. Capiau's opinion that the disclosure of "a monoclonal immunoglobulin specific for ACAP" was "adequate" for purposes of the best mode requirement. *Cf.* Fonar v. General Elec. Co., 107 F.3d 1543, 1549 (Fed.Cir.1997) ("It is well established that what is within the skill of the art need not be disclosed to satisfy the best mode requirement as long as that mode is described.") Accordingly, it is for a jury to determine whether the U.S. application disclosed a method sufficiently comparable to that actually employed by Novotny, or whether it was so objectively inadequate as to effectively conceal the best mode from the public.

b. *Hybridoma Deposit*

[18] Even if the original U.S. application did not sufficiently disclose BB05, this deficiency may have been cured by the subsequent hybridoma deposit and concomitant amendment to the specification. In January 1990, a hybridoma that secretes BB05 was deposited at the European Collection of Animal Cell Cultures under the Budapest Treaty. This deposit was made nearly five years after the filing of the original U.S. application. Over two years after the deposit was made, the specifications of the patents in suit were amended to include the following reference to the deposit: "The hybridoma which secretes the monoclonal immunoglobulin was deposited under the Budapest Treaty at the European Collection of Animal Cell Cultures, Porton Down, United Kingdom on January 5, 1990 under accession number 90010501." Both the deposit and this reference predated the issuance of the patents.

At issue is whether the belated deposit satisfies the best mode requirement by curing what for present purposes is presumed to be a deficiency in the original application. In effect, plaintiffs suggest two alternative ways in which the deposit may have cured the best mode defect (assuming there was such a defect). First, the deposit may have supplemented the preexisting disclosure in the original application of "a monoclonal immunoglobulin specific for ACAP." Under this view, the original application at least mentioned the antibody, even if it did not adequately describe it; the deposit, then, simply supplemented this reference and cured any deficiency. Second, the deposit may have satisfied the best mode requirement in conjunction with the amendment of the original application. Under this view, even if the deposit fails to cure the best mode defect in conjunction with the language of the original application, it satisfies the best mode requirement in conjunction with the amended language.

Under either view, both sides rely heavily on In re Lundak, 773 F.2d 1216 (Fed.Cir.1985), which concerned when, if ever, a belated deposit of biological material can satisfy the enablement (not the best mode) requirement. In *Lundak,* the original application claimed a new human cell line and the specification disclosed (over the course of twelve pages) the procedures for producing it. At the time the inventor filed the

application, he believed that samples of his new cell line had already been deposited in a biological materials depository. However, the deposit was not made until seven days after the filing. *See id*. at 1217-18.

The Court of Appeals held that the delay in making the deposit did not invalidate the patent. The court began by identifying the primary interests served by the enablement requirement-the PTO's interest in access to a deposit during the pendency of a patent application for purposes of administering the patent statute, and the public's interest in a complete, enabling disclosure. *See id*. at 1221-22. It then concluded that the enablement requirement

... does not require the transfer of a sample of the invention to an independent depository prior to the filing date of the patent application. The requirements of PTO access to a sample of Lundak's cell line during pendency, and public access after grant, were met by Lundak's procedures. Lundak's deposit ..., which was made after filing but prior to issuance of his patent, and which is referred to in his specification, meets the statutory requirements.

Id. at 1222.

Defendants argue that *Lundak* is not applicable where, as here, the original application contained no description of the BB05 monoclonal antibody or a method of producing it, but instead applies only where the original application provides a complete description of the deposited material. Plaintiffs contend that *Lundak* "held that if any biomaterial referenced in a specification was in existence as of the filing date, then it may be deposited" to satisfy the best mode requirement. (Pls.' Reply Mem. in Supp. of Deposit & Foreign Priority Mot. at 3.) Contrary to defendants' position, plaintiffs assert that the U.S. specification as filed contained a reference to the deposited material-"a monoclonal immunoglobulin specific for ACAP"-sufficient for best mode purposes.FN11

FN11. Both sides refer to the PTO's examination procedures for biological deposits to shed light on *Lundak* 's holding. At the time of Novotny's deposit (*i.e.*, pre- *Lundak*), the PTO's Manual of Patent Examining Procedure ("MPEP") indicated that the PTO would accept a deposit of a microorganism as complying with 35 U.S.C. s. 112 if, *inter alia:* (1) "the applicant, *no later than the effective U.S. filing date of the application,* has made a deposit of a culture of the microorganism in a depository;" and (2) " *such deposit is referred to in the body of the specification as filed* ..., and the taxonomic description to the extent available is included in the specification." MPEP s. 608.01(p)C, at 600-36 (1983) (emphasis added). After *Lundak,* the PTO cited that case in revising these guidelines to state that it would "accept the deposit of a suitable microorganism or other biological material made *after* the effective U.S. filing date of the application so long as the microorganism or other biological material is *identified in the application as filed* and a suitable deposit is made before the patent is granted." MPEP s. 608.01(p)C, at 600-44 (1988) (emphasis added).

Whether the reference to "a monoclonal immunoglobulin specific for ACAP" is sufficient to permit the subsequent deposit to satisfy the best mode requirement depends in part upon how one reads *Lundak*. Plaintiffs contend that *Lundak* merely requires a "reference" to the deposited material, and point to Novotny's declaration that the phrase "a monoclonal immunoglobulin specific for ACAP" refers to the subsequently deposited material. Defendants argue that *Lundak* requires far more than a brief reference to the deposited material, particularly where that reference identifies the material only in broad terms. They point out that in *Lundak,* the best mode disclosure contained a detailed description of both the new cell line

and how to produce it. By contrast, they argue, the specification in this case mentioned only "a monoclonal immunoglobulin specific for ACAP" rather than BB05 specifically, and did not even attempt to describe the antibody or how to produce it.

Aside from the obvious fact that *Lundak* involved the enablement requirement and not the best mode requirement, it is significant that the deposit in *Lundak* merely supplemented a sufficiently detailed written description of the specimen and the procedures by which it was developed. However, the Court need not-indeed, as discussed above, it cannot-definitively resolve the issue of the adequacy of the reference to "a monoclonal immunoglobulin specific for ACAP" for purposes of the *Lundak* analysis. Instead, the Court concludes, as discussed below, that the combination of the belated deposit and the amendment of the specification to refer to that deposit satisfies the best mode requirement as a matter of law.

While it is clear that the subjective component of the best mode requirement focuses on the inventor's state of mind at the time the patent application is filed, it is unclear whether the objective component automatically renders a patent invalid if a reference to the best mode is added to the specification after the original filing date. Dicta in opinions of the Federal Circuit can be read to support either view. *Compare* Brooktree Corp. v. Advanced Micro Devices, Inc., 977 F.2d 1555, 1575 (Fed.Cir.1992) ("That which is included in an issued patent is, *ipso facto,* not concealed.") *with* Amgen, 927 F.2d at 1210 ("One must not receive the right to exclude others unless at the time of filing he has provided an adequate disclosure of the best mode known to him of carrying out his invention.").FN12 However, these cases do not directly address the issue at hand, and none has held that a deficient best mode disclosure cannot be cured by a deposit of a specimen before issuance of the patent.

FN12. *See also* Carter-Wallace, Inc. v. Riverton Lab., Inc., 433 F.2d 1034, 1038 (2d Cir.1970) ("the critical date with regard to disclosing the best mode contemplated is the date of the filing of the application").

The Court can discern no reason why a belated deposit of biological material, in conjunction with a reference to that deposit added to the specification prior to issuance, should not be deemed to comply with the best mode requirement. Neither statutory language nor case law nor policy considerations requires a ruling to the contrary. To begin with, the language of the statute merely states that the "specification ... shall set forth the best mode contemplated by the inventor of carrying out his invention." 35 U.S .C. s. 112, para. 1. It does not address whether an initially deficient specification may be cured. Moreover, defendants have not cited, and the Court has not found, any case holding that a best mode defect cannot be cured before issuance.

In addition, the Federal Circuit has repeatedly stated that "the sole purpose of [the best mode] requirement is to restrain inventors from applying for patents while at the same time concealing from the public preferred embodiments of their inventions which they have in fact conceived." U.S. Gypsum, 74 F.3d at 1215 (quoting In re Gay, 50 C.C.P.A. 725, 309 F.2d 769, 772 (Cust.& Pat.App.1962)); *accord* Glaxo Inc. v. Novopharm Ltd., 52 F.3d 1043, 1050 (Fed.Cir.1995); Chemcast, 913 F.2d at 926. Because the public does not have access to a specification and its stated best mode until after the patent issues, the public interest in access to the best mode is not contravened as long as the specification, as issued, adequately discloses the inventor's contemplated best mode. *Cf.* Lundak, 773 F.2d at 1221 ("As for assuring public access, ... 'the enablement requirement of s. 112, first paragraph, does not require such assured access to a microorganism deposit as of the filing date; what is required is assurance of access (to the microorganism culture by the public upon issuance of a patent on the application) prior to or during the pendency of the application, so

that, upon issuance of a U.S. patent on the application, the public will, in fact, receive something in return for the patent grant.' ") (quoting *Feldman v. Aunstrup,* 517 F.2d 1351, 1355 (Cust.&Pat.App.1975)); *id.* at 1223 ("[T]he function of section 112 in ensuring complete public disclosure is only violated if the disclosure is not complete at the time it is made public, *i.e.,* at the issue date.") (quoting *In re Hawkins,* 486 F.2d 569, 574 (Cust.&Pat.App.1973)); 4 CHISUM ON PATENTS s. 13.04[2] n.1.1, at 13-27 (1998) ("Arguably, the purposes of the best mode requirement are met if the best mode is in fact set forth in the specification as of the date the patent issues.").

To the extent that the best mode requirement also may implicate the interests of the PTO,FN13 it is conceivable that a failure to disclose the best mode could hamper an Examiner in his or her examination and prior art search. In general, this seems unlikely; in this particular case, there is no indication that the delay in complying with the best mode requirement had any impact on the PTO's interests.

FN13. Arguably, in contrast to the enablement issue, the PTO's interests are of little or no relevance in the best mode inquiry. *Compare* Lundak, 773 F.2d at 1222 (enablement implicates the PTO's interest in access during pendency of an application and the public interest in access after issuance) *with* U.S. Gypsum, 74 F.3d at 1215 (best mode requirement's "sole purpose" is to prevent inventors from concealing a best mode "from the public"); Glaxo, 52 F.3d at 1050 (same) *and* Chemcast, 913 F.2d at 926 (same).

Therefore, even if a jury were to find that Novotny contemplated BB05 as the best mode and that the reference in the original specification to "a monoclonal immunoglobulin specific for ACAP" was itself inadequate to support the subsequent hybridoma deposit, the deposit and the reference to it in the amended specification constitutes an adequatebest mode disclosure as a matter of law.FN14

FN14. This can be determined as a matter of law because defendants have not argued that, even if the belated deposit and amended reference legally can cure the initially defective best mode disclosure, those subsequent disclosures nevertheless were objectively inadequate, which would pose a factual issue. In other words, the dispute with respect to the second, objective component of the best mode inquiry into the sufficiency of the hybridoma deposit involves only the legal effect, if any, of the belated disclosures.

Accordingly, to the extent that defendants seek a summary determination of invalidity for failure to comply with the best mode requirement, their motion is denied. To the extent that plaintiffs' motion for partial summary judgment seeks a determination that the hybridoma deposit and subsequent amendment to the specification satisfied the best mode requirement, it is granted.

B. *Invalidity based on Prior Art*

Defendants have asserted an affirmative defense that the patents in suit are invalid because the claimed subject matter is anticipated by or obvious in view of various prior patents and publications. Plaintiffs move for partial summary judgment that these references do not anticipate the claimed inventions.

[19] Section 102(a) provides that a patent is invalid if "the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for patent." 35 U.S.C. s. 102(a).FN15 From this provision springs the doctrine of anticipation: "That which would literally infringe if later in time anticipates if earlier than the date of

invention." Lewmar Marine, Inc. v. Barient, Inc., 827 F.2d 744, 747 (Fed.Cir.1987).

FN15. Similarly, s. 102(b) provides that a patent is invalid if the claimed process was "described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States ...." 35 U.S.C. s. 102(b).

[20] [21] [22] More specifically, anticipation under s. 102(a) "requires the presence in a single prior art disclosure of each and every element of a claimed invention." *Id.; accord* Glaverbel Societe Anonyme v. Northlake Mktg. & Supply, Inc., 45 F.3d 1550, 1554 (Fed.Cir.1995) ("Anticipation requires identity of the claimed process and a process of the prior art; the claimed process, including each step thereof, must have been described or embodied, either expressly or inherently, in a single reference."); Diversitech Corp. v. Century Steps, Inc., 850 F.2d 675, 677 (Fed.Cir.1988) ("every element of the claimed invention must be identically shown in a single reference"). There must be no difference between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the field of the invention. Scripps Clinic & Research Found. v. Genentech, Inc., 927 F.2d 1565, 1576 (Fed.Cir.1991); *accord* In re Spada, 911 F.2d 705, 708 (Fed.Cir.1990) ("the reference must describe the applicant's invention sufficiently to have placed a person of ordinary skill in the field of the invention in possession of it"). Anticipation is a question of fact and must be demonstrated by a patent challenger by clear and convincing evidence. Diversitech, 850 F.2d at 677.

1. ***Takeda Prior Art***

[23] [24] Whether the Takeda patent and the Takeda antigen (collectively, the "Takeda prior art") anticipate the patents in suit is the mirror image of the infringement question. *See* Lewmar Marine, 827 F.2d at 747 ("The inquiry as to anticipation is symmetrical with the inquiry as to infringement of a patent."). As discussed above, because Takeda's vaccine is a mixture of many antigens in which 69k constitutes only 4%, and because it has no adenylate cyclase activity, it does not come within the scope of any of the claims of the patents in suit as construed by the Court. Under this construction, it is irrelevant whether the Takeda antigen shipped to the U.S. was on sale or in use within the meaning of 35 U.S.C. s. 102,FN16 or contained "small amounts of pertactin." For the same reasons, the Takeda patent, which discloses the Takeda antigen, does not anticipate any of the claims of the patents in suit. Therefore, with respect to the Takeda prior art, defendants' motion for summary judgment of invalidity is denied and plaintiffs' motion for partial summary judgment is granted.

FN16. A "use[ ]" under s. 102(a) must be a public use. *See* Carella v. Starlight Archery & Pro Line Co., 804 F.2d 135, 139 (Fed.Cir.1986); W.L. Gore & Assoc., Inc. v. Garlock, Inc., 721 F.2d 1540, 1549 (Fed.Cir.1983).

[25] Even if the Court were to adopt plaintiffs' interpretation of the claims, defendants' motion for summary judgment of invalidity based on the Takeda prior art would have to be denied. This is because there exists a material question of fact whether the antigen produced by Takeda's pre-gel process, which was shipped to the U.S. in late 1982 and early 1983, contained 69k. The pertinent facts are as follows. Between October 1982 and February 1983, Takeda shipped four lots of its antigen to Wyeth Laboratories ("Wyeth"), a Pennsylvania-based subsidiary of defendant American Home Products, which then developed a diphtheria-tetanus-acellular pertussis ("DTaP") vaccine containing the antigen. On August 8, 1983, Wyeth conducted

an animal potency test of the vaccine, and in November 1983 and April 1984 conducted two animal safety tests. Between December 1983 and April 1984, Wyeth sent at least 50 tubes of DTaP to the FDA in connection with an investigational new drug ("IND") application. Upon receiving FDA authorization in May 1984 to test the vaccine, Wyeth began inoculating children with it, first on May 8 and again on May 10.

While the above facts are undisputed, the parties contest the nature and purpose of the shipments to Wyeth. Defendants contend that Takeda had agreed to license its antigen to Wyeth and that the shipments were sold to Wyeth for commercial purposes. Plaintiffs, on the other hand, claim that the lots were sent subject to a confidentiality agreement and were for experimental use only. Additionally, plaintiffs argue that even if the lots were on sale or in use in the U.S. prior to the effective date, the lots did not inherently contain 69K, and therefore are not prior art.

[26] [27] Whether an invention is on sale or in use is a question of law based upon the totality of the circumstances. Continental Plastic Containers v. Owens Brockway Plastic Prod., Inc., 141 F.3d 1073, 1077 (Fed.Cir.1998); Manville Sales Corp. v. Paramount Sys., Inc., 917 F.2d 544, 549 (Fed.Cir.1990). This determination must be supported by clear and convincing evidence. *See* Baxter Int'l, Inc. v. Cobe Lab., Inc., 88 F.3d 1054, 1059 (Fed.Cir.1996); Ferag AG v. Quipp Inc., 45 F.3d 1562, 1566, 1569 (Fed.Cir.1995). Factors which the court considers include the existence of secrecy obligations, any record keeping of claimed experiments, the number of tests, the length of the testing period, the extent of control of the inventor over the claimed experimentation, any attempts to market the invention, and whether payment was received for the invention. U.S. Envtl. Prod. Inc. v. Westall, 911 F.2d 713, 717 (Fed.Cir.1990); Baker Oil Tools, Inc. v. Geo Vann, Inc., 828 F.2d 1558, 1564 (Fed.Cir.1987). Although "[t]his list of factors is by no means all inclusive, [it] serves as a basis for objective analysis ...." In re Brigance, 792 F.2d 1103, 1108 (Fed.Cir.1986). After thorough consideration, the Court concludes that clear and convincing evidence establishes that Takeda's antigen was on sale in this country as early as 1982, and in use no later than May 8, 1984.

First, the evidence indicates that the antigen was on sale prior to the application date of the patents in suit.FN17 It is undisputed that Takeda sent four shipments of antigen to Pennsylvania between November 1982 and February 1983. While plaintiffs contend that there is no evidence that Wyeth actually paid for these shipments, the invoices indicate that Wyeth was charged 1.4 million yen for the vaccine. (*See* Deitch Decl., Exhs. 5, 6.) In any event, whether or not Wyeth paid for the lots is not controlling. *See* Baker Oil Tools, 828 F.2d at 1564.FN18

FN17. As discussed below in Part III.B.2, the parties dispute the priority date of the U.S. parent application. For the purposes of determining whether the antigen was on sale under s. 102(b) or used under s. 102(a) prior to the effective date, it is irrelevant whether the U.S. application (filed on May 1, 1985) is entitled to the priority date of the U.K. application (May 12, 1984), as the events pertinent to this discussion each occurred prior to May 12, 1984.

FN18. Plaintiffs also make much of the fact that the invoices state that the antigen has "no commercial value." However, the Court declines to hold, based on this lone statement, that the lots were shipped for experimental purposes only. At most, the statement is ambiguous, when considered in light of the remaining evidence. *See* Evans Cooling Sys., Inc. v. General Motors Corp., 125 F.3d 1448, 1451 (Fed.Cir.1997), *cert. denied,* 522 U.S. 1115, 118 S.Ct. 1050, 140 L.Ed.2d 113 (1998); Paragon Podiatry Lab., Inc. v. KLM Lab.,

Inc., 984 F.2d 1182, 1188 (Fed.Cir.1993). More likely, because the invoices were prepared by Wyeth on Wyeth letterhead, it was Wyeth that determined that the lots had no commercial value. (*See* Deitch Decl., Exhs. 5, 6.) The key inquiry is how Takeda, not Wyeth, valued the vaccine and meant it to be used. *See* Seal-Flex, Inc. v. Athletic Track & Court Constr., 98 F.3d 1318, 1324 (Fed.Cir.1996).

Second, the evidence does not support plaintiffs' contention that the shipments were subject to secrecy. Although Takeda entered into a confidentiality agreement with Wyeth regarding information obtained by Wyeth during on-site visits to Takeda's plant, the agreement on its face is limited to information obtained during these visits. (*See* Pls.' Mem. in Opp. to Takeda Prior Art Mot., Exh. 20.) Plaintiffs present no other evidence of secrecy obligations between Wyeth and Takeda, and in particular, no evidence that the lots shipped to Wyeth were subject to a confidentiality agreement. *See* U.S. Envtl. Prod., 911 F.2d at 717 (no confidentiality agreement where initial proposal contained restrictions on use but final offer to sell had no such provision).FN19 In fact, as defendants point out, the composition of DTaP was disclosed by letter to the parents of children inoculated with the vaccine in May 1984, including the presence of the Takeda antigen, along with a history of the antigen's use in Japan. (*See* Second Deitch Decl. para.para. 4-5, Exh. 1.)

FN19. The fact that Wyeth typically entered into confidentiality agreements upon exchanging proprietary information, (*see* Saldarini Dep. at 56-57), is not particularly helpful here. In his deposition, Wyeth CEO Dr. Ronald Saldarini did not recall whether Wyeth had such an agreement with Takeda. In any case, the scope of the agreements at issue during Saldarini's deposition is unclear from the excerpts cited by plaintiffs. (*See id.*) The Court notes that the parties have not submitted copies of the agreements, or other documentation, used by plaintiffs during the deposition to attempt to refresh Saldarini's recollection.

Moreover, the fact that there may have been a confidentiality agreement between Wyeth and UCLA is besides the point. What matters here is whether Takeda intended to keep information about its antigen confidential, once it had entered the United States. Clearly, it did not.
Third, there is no evidence that Takeda retained control over the tests performed by Wyeth. While Takeda was to be advised of the results of the testing, (*see* Deitch Decl., Exh. 5), there is nothing in the record to indicate that Takeda monitored the testing procedures. Because one of the policies underlying experimental use is to allow the inventor "sufficient time to test an invention before applying for a patent," "the inventor's lack of direction or control over ... use of the invention ... supports a conclusion that the use was not experimental." Baxter, 88 F.3d at 1060.

Thus, a review of the evidence clearly shows that plaintiffs are wrong in contending that Takeda shipped its antigen to Wyeth in order to test it. Rather, the evidence conclusively establishes that Takeda had fully tested and successfully marketed its vaccine in Japan, beginning in 1981. (*See* Second Deitch Decl., Exh. 2 ("In the last several years in Japan, several acellular vaccines have been prepared and are being routinely used in the immunization of children.").) There is no apparent reason why Takeda, after having established the efficacy and safety of its vaccine in Japan, would retest its vaccine in the United States, for any reason other than to obtain FDA approval for its sale and use here. (*See* Second Deitch Decl., Exh. 1 ("This ... vaccine ... *has been extensively tested in Japan*.") (emphasis added)). *Cf.* Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1570 (Fed.Cir.1997) (affirming finding of prior art where public was aware of capabilities of invention, while underlying software was proprietary and confidential); Paragon, 984 F.2d at 1187 (no experimental use where letters sent to doctors stated that product was "culmination of *extensive research and exhaustive clinical testing* ") (emphasis in original). Nor do plaintiffs suggest-and the Court

cannot think of any reason to infer-that children inoculated with the vaccine in the United States would respond differently to it than children inoculated in Japan. *Compare* Petrolite Corp. v. Baker Hughes Inc., 96 F.3d 1423, 1427 (Fed.Cir.1996) (patent invalid under s. 102(b) where inventor had successfully tested product, even though additional tests were necessary to verify reliability; no evidence to suggest that product would perform differently in colder climates) *with* Allied Colloids Inc. v. American Cyanamid Co., 64 F.3d 1570, 1576 (Fed.Cir.1995) (no bar under s. 102(b) where composition of sewage varied from place to place) *and* Manville Sales, 917 F.2d at 550-51 (no bar under s. 102(b) where lighting pole had to be tested outdoors with "cold, rain, snow, and wind"). The literature confirms this. (*See, e.g.,* Second Deitch Decl., Exh. 2 ("From experimental data from Japan it is anticipated that immunization ... is likely to be associated with a lessening of local reactions at the vaccination site and decreased febrile response.").)

[28] Finally, the fact that Wyeth had formulated a new vaccine by adding Takeda's antigen to its own diphtheria-tetanus mixture cannot be discounted. DTaP, the resulting product, was not the same vaccine as Takeda's, no matter how the parties view the composition of the Takeda antigen. Testing additional uses of an already existing product is not an "experimental use" under s. 102. *See* Baxter, 88 F.3d at 1060 (public use where original design was modified by third party and used exclusively by third party in laboratory, because inventor had no control over modifications).

While Takeda's antigen was on sale and in use in this country prior to the earliest claimed effective filing date of the patents in suit, the Court would nonetheless deny summary judgment to defendants because there remains a material issue of fact whether 69K was present in the lots shipped to Wyeth. To establish the presence of 69K, defendants point to tests which allegedly show at least small amounts of pertactin in Lots 13 and 14, two of the lots sent to Wyeth during 1982-83. These tests suggest that many of the lots produced prior to 1986 contained at least small amounts of 69K, and that children immunized with the Takeda antigen in May 1984 developed antibodies to pertactin. (*See* Falkow Decl. para.para. 7, 8(a).)

Plaintiffs, on the other hand, rely on tests which circumstantially suggest that 69K could not have been present in some of the pre-gel samples, because other, recognizable proteins reportedly constituted 100% of the samples. Plaintiffs further assert that their tests show that two of the lots sent to Wyeth, Lot 014 and Lot B 119, did not contain 69K, because no band denominating the protein appeared on PAGE analysis. (*See* Pls.' Mem. in Opp. to Takeda Prior Art Mot. at 13.) Defendants challenge the accuracy of these tests because in some cases, the other proteins added up to more than 100%. Defendants also contend that the failure to find pertactin in the samples proves nothing because the tests were "designed to establish the presence and measure the amounts of other antigens, before there was an antibody test to detect the presence or absence of pertactin and before pertactin was recognized as a component of *B*. pertussis." (Defs.' Mem. in Supp. of Takeda Prior Art Mot. at 18.)

Because the results of these tests are in conflict, and interpretation of the evidence "depend[s] on the assessment of scientific facts as well as on the credibility of witnesses, [the Takeda prior art issues] are not amenable to summary resolution." Scripps, 927 F.2d at 1574. Thus, even under plaintiffs' construction of the claims, the Court would deny summary judgment with respect to the Takeda prior art.

2. *The Montaraz et al. Article*

Defendants contend that the Montaraz et al. article (Exh. 20) invalidates the claims of the '052 and '120 patents on the ground of anticipation and the claims of the '080 patent on the ground of obviousness. The article, which was published between the filing dates of the U.K. application (May 12, 1984) and the U.S.

application (May 1, 1985), disclosed the process of raising the BB05 monoclonal antibody and using it in an immunosorbent column to purify antigens extracted from the outer membrane of *B. bronchiseptica* cells. Plaintiffs contend that this article does not constitute prior art because the U.S. application is entitled to the priority date of the U.K. application, which antedates the article.

The threshold question, therefore, is whether the domestic application is entitled to the priority date of the foreign application as provided in 35 U.S.C. s. 119(a).FN20 *See* In re Gosteli, 872 F.2d 1008, 1010 (Fed.Cir.1989) ("Generally, an applicant may antedate prior art by relying on the benefit of a previously filed foreign application to establish an effective date earlier than that of the reference."). The benefit of a foreign priority date can be obtained only for those claims in the domestic application (or the issued patents) that are adequately supported by the foreign application within the requirements of the first paragraph of s. 112. *See id.* at 1010-11.

FN20. Section 119(a) provides in pertinent part:
An application for patent for an invention filed in this country by any person who has ... previously regularly filed an application for a patent for the same invention in a foreign country ... shall have the same effect as the same application would have if filed in this country on the date on which the application for patent for the same invention was first filed in such foreign country ....

35 U.S.C. s. 119(a) (West Supp.1998).
[29] [30] [31] Defendants focus primarily on the "written description" requirement of the first paragraph of s. 112, arguing that the description in the U.K. application fails to support the invention claimed in the U.S. application. The purpose of the written description requirement is to "guard [ ] against the inventor's overreaching by insisting that he recount his invention in such detail that his future claims can be determined to be encompassed within his original creation." Vas-Cath Inc. v. Mahurkar, 935 F.2d 1555, 1561 (Fed.Cir.1991) (citation omitted).FN21 Although, for purposes of sections 119 and 112, a prior foreign application does not have to describe exactly the subject matter claimed in the domestic application, its written description must clearly indicate to persons skilled in the art that, as of the foreign filing date, the applicant had invented what is claimed in the domestic application. *See* Eiselstein v. Frank, 52 F.3d 1035, 1039 (Fed.Cir.1995); Vas-Cath, 935 F.2d at 1563-64; Gosteli, 872 F.2d at 1012. Whether the written description requirement is met is a question of fact. In re Alton, 76 F.3d 1168, 1171-72 (Fed.Cir.1996); Vas-Cath, 935 F.2d at 1563.

FN21. *See also* id. at 1562 ("Satisfaction of the [written] description requirement insures that subject matter presented in the form of a claim subsequent to the filing date of the application was sufficiently disclosed at the time of filing so that the prima facie date of invention can fairly be held to be the filing date of the application.") (citation omitted).

The U.K. application describes a new use and recovery method for adenylate cyclase, a substance already known in the prior art.FN22 It explains that the newly discovered capability of adenylate cyclase enables production of an improved *B.* pertussis vaccine:

FN22. The U.K. application distinguished the claimed invention from this prior art product by stating that "[a]denylate cyclase has been previously isolated from *B. pertussis* ... but there has not yet been any suggestion that this material represents the major protective antigen against *B. pertussis*."

... We have now discovered that adenylate cyclase, an enzyme found in the cultures of *B*. pertussis, is capable of providing protection against challenge by *B*. pertussis in experimental animals. This discovery that adenylate cyclase is a major protective antigen against *B*. pertussis permits the preparation of vaccine formulations comprising antigenic preparations which are free from, or contain reduced amounts of, other *B*. pertussis components which are responsible for the toxic side-effects demonstrated by whole cell vaccines. According to one feature of the present invention we provide a vaccine formulation for protection against *B*. pertussis which includes an antigenic preparation comprising adenylate cyclase ... together with an adjuvant and/or carrier for the said antigenic preparation.

* * * * * *

According to a further feature of the present invention we provide a method for the isolation of an antigenic preparation containing adenylate cyclase from *B*. pertussis ....

As previously discussed, this description indicates that at the time the U.K. application was filed, Novotny believed that the antigen whose immunogenic effects he had discovered was adenylate cyclase. (*See* Novotny Dep., June 4, 1997, Exh. 50 at 7, 44.) Subsequently, Novotny "started to be suspicious" that the antigen was not adenylate cyclase, and was uncertain of its identity. (*Id*. at 44.)

Accordingly, while the description of the invention in the U.S. application largely duplicated that in the prior U.K. application, it also reflected Novotny's new knowledge that the antigen being studied was not adenylate cyclase and his lingering uncertainty as to its actual identity:

It has now been discovered that certain proteinaceous material associated with adenylate cyclase activity, as hereinafter described, found in the cultures of *B*. pertussis, is capable of providing protection against challenge by *B*. pertussis when administered to experimental animals. This discovery that the proteinaceous material usually associated with adenylate cyclase activity is a major protective antigen against *B*. pertussis permits the preparation of vaccine formulations comprising antigenic preparations which are free from, or contain reduced amounts of, other known *B*. pertussis components which may be responsible for the toxic side-effects demonstrated by whole cell vaccines.

The term 'proteinaceous material associated with adenylate cyclase activity' (abbreviated to 'ACAP' hereinafter) is used herein to refer to proteinaceous material which is extracted together with adenylate cyclase activity when extraction of the adenylate cyclase activity is performed using an aqueous, acidic (pH3) solution of glycine (0.25 M). The ACAP as defined above may comprise the adenylate cyclase enzyme *per se* or a binding protein for the enzyme.

* * * * * *

In a first feature of the present invention is provided a vaccine formulation for protection against *B*. pertussis which includes an antigenic preparation derived from *B*. pertussis comprising ACAP ... together with a pharmaceutically acceptable carrier therefor.

* * * * * *

... in an alternative aspect of the present invention is provided a method for the isolation of an antigenic preparation containing ACAP from *B*. pertussis ....

Thus, the U.K. specification describes a new use and recovery method for a known substance (adenylate cyclase), while the U.S. patents disclose and claim a new antigen (ACAP or 69k) not known in the prior art.

The parent U.S. application is entitled to the benefit of the filing date of the U.K. specification only if that specification would clearly indicate to a person skilled in the art that, as of the foreign filing date, Novotny had invented (or was in "possession" of) the subject matter claimed in the U.S. application. *See* Vas-Cath, 935 F.2d at 1563. This question involves a comparison not of the descriptions contained in the U.K. and U.S. applications, but of the description in the U.K. application and the claims, as construed by this Court, in the issued U.S. patents.

The U.S. patents in suit claim a purified *B*. pertussis antigen having specified characteristics, and a vaccine based on that antigen. The pivotal question is whether the U.K. specification would clearly inform a person skilled in the art that Novotny had discovered that specific claimed antigen. However unlikely this may appear, it nevertheless is the opinion expressed by plaintiffs' employee/expert, Dr. Capiau. (*See* Capiau Decl. para. 20, Exh. 1 to Pls.' Mem. in Opp. to Montaraz Mot.) This raises the factual issue of whether the foreign application adequately supports the domestic claims as construed by the Court, a question which must be left for the jury.FN23 *See* Alton, 76 F.3d at 1171-72; Vas-Cath, 935 F.2d at 1563.

FN23. If the Court were to construe the patent claims as plaintiffs urge- *i.e.,* as covering antigens having no adenylate cyclase activity-the support of those claims by Novotny's U.K. specification would become much more tenuous, because that specification identifies Novotny's discovery as adenylate cyclase *per se*. Thus, plaintiffs must negotiate a precarious passage between the Scylla of non-infringement and the Charybdis of invalidity in view of the Montaraz et al. article. If they steer clear of one of those hazards, they substantially increase their risk of foundering on the other.

[32] However, even if a jury were to conclude that the patents are not entitled to the earlier priority date, the Montaraz et al. article would not necessarily constitute prior art. For purposes of anticipation under s. 102(a), an inventor's own work is not prior art even though it has been publicly disclosed prior to the application. Specialty Composites v. Cabot Corp., 845 F.2d 981, 990 n. 9 (Fed.Cir.1988); In re Costello, 717 F.2d 1346, 1349 (Fed.Cir.1983); In re Katz, 687 F.2d 450, 454-55 (Cust.& Pat.App.1982); *In re DeBaun,* 687 F.2d 459, 462 (Cust.&Pat.App.1982). FN24 Thus, if Montaraz were a co-inventor with respect to the patents in suit, the Montaraz et al. article would not be prior art and could not invalidate the patents. With this in mind, plaintiffs have responded to defendants' motion for summary judgment of invalidity based on the Montaraz et al. article by moving under 35 U.S.C. s. 256 to "correct inventorship" by adding Montaraz as a co-inventor of the patents in suit.

FN24. This assumes, of course, the absence of a time bar under s. 102(b). *See* Specialty Composites, 845 F.2d at 990 n. 9; Katz, 687 F.2d at 454-55.

Without deciding plaintiffs' s. 256 motion, the Court notes its doubt as to the merit of that motion. In particular, the Court is troubled by (1) Novotny's previous declaration that he is "the inventor" of the inventions described in the parent application and that Montaraz "worked under my supervision and made

no contribution to the conception of any part of the invention(s) claimed in the present application," (Novotny Decl., Exh. 9 to Defs.' Mem. in Opp. to s. 256 Mot.); (2) the fact that at no point has Montaraz ever stated that he should have been named as an inventor; and (3) plaintiffs' continued failure to raise this issue previously despite the obvious incentive to do so.

Defendants' motion for summary judgment of non-infringement having been granted, there is no reason for the Court now to rule on plaintiffs' motion to add Montaraz as a co-inventor on the patents in suit. Indeed, even if the grant of summary judgment should be reversed on appeal, there would be no need to add Montaraz as a co-inventor unless and until it should be ruled that the U.S. patents are not entitled to the priority date of the U.K. application. If it is finally ruled otherwise, plaintiffs may even wish to withdraw the motion.

For the present, suffice it to say that defendants' motion for summary judgment of invalidity based on the Montaraz et al. article is denied.

3. ***Other Prior Art***

[33] Defendants have asserted an affirmative defense that the patents in suit are invalid under 35 U.S.C. s.s. 102 and 103 because the claimed inventions were anticipated by or obvious in view of the disclosures of a number of prior patents and publications. Plaintiffs move for partial summary judgment that none of these references anticipates the claimed inventions.

As discussed hereinafter, each of these references discloses the extraction of antigens from the outer membrane of *B*. pertussis (or, in one reference, *H*. pertussis) cells. None of the references discusses the use of the extracted antigens in a pertussis vaccine, although such an application might reasonably be presumed. In some of the references, for example, the immediate object of the procedure disclosed was merely to recover adenylate cyclase and measure its enzymatic activity. However, defendants contend that the procedure employed in each case would inevitably result in the extraction of *some* quantity of 69k. Defendants thus argue that, if the patent claims are construed to cover vaccines and antigens which contain *any* significant amount of 69k, as plaintiffs urge, the claims are anticipated by each of the references.

In deciding plaintiffs' motion for summary judgment that none of the references anticipates the claimed invention, the Court must of course give the claims the same construction which it gave them in resolving the issue of infringement. That is, each of the claims will be construed as requiring an antigenic preparation in which 69k constitutes at least 50% of the composition, and which has a proline:glutamic acid ratio between 0.95:1 and 1.05:1, and adenylate cyclase activity.

Although some of the references discuss adenylate cyclase activity, none of them discusses 69k as such, much less discloses the concentration of 69k in the mixture of extracted proteinaceous material or its proline:glutamic acid ratio. Thus none of them even comes close to a specific disclosure of the invention covered by any of the claims as construed by the Court. On the basis of its construction of the claims, the Court will therefore grant plaintiffs' motion for summary judgment that none of these references anticipates the invention covered by any of the claims of the patents in suit. This decision is, of course, subject to reconsideration in the event that appellate review results in a different construction of the claims. And, of course, the Court's decision has no application to defendants' affirmative defense under s. 103 that the claims are invalid for obviousness in view of the disclosures of these references.

In the ensuing discussion of the several references, additional reasons why they do not anticipate the claimed inventions will be mentioned.

a. *The Dahlstrom patent*

This prior U.S. patent (Exh. 6) teaches "an improved method" for the preparation of a *B*. pertussis antigen which is "essentially free from cell debris and other substances ...." The antigen is extracted from the outer membrane of *B*. pertussis cells by treatment with saline solution at a pH of about 10. The resulting solution is neutralized with sterile acid and centrifuged to remove the cells.

Apparently, this procedure inherently and inevitably produces an antigenic mixture which includes some 69k, because Dahlstrom represents that it provides "long-term immunity against whooping cough." Indeed, that was the conclusion reached by the PTO Examiner handling the applications for the patents in suit, who accordingly rejected the claims until they were amended to limit them to a "purified" 69k.

The Court has construed this claim limitation so that it does not read on the Dahlstrom patent, as it must be construed to preserve its validity.

b. *Pillemer, PROC. SOC'Y EXPERIMENTAL BIOLOGY AND MED. 75:704-05 (1950)*

This article (Gram Aff., Exh. D) reports the results of experiments to determine whether the protective antigen of *Hemophilus* pertussis (" *H.pertussis* ") can be adsorbed on human red cell stromata without loss of potency. The article discloses a process of isolating the antigen which involves sonic disintegration of *H*. pertussis cells and removing the debris by centrifugation.

The article does not mention 69k, much less its concentration in the antigenic mixture produced. Indeed, no evidence has been submitted to the Court to establish that 69k can be extracted from *H*. pertussis (as distinguished from *B*. pertussis) cells.

c. *Novotny & Brookes, J. BIOLOGICAL STANDARDIZATION 3:11-29 (1975)*

This article (Gram Aff., Exh. E) discloses the freezing in liquid nitrogen of an antigen, prepared as described in the Pillemer article just discussed, to determine whether this affected its immunogenic potency in a Kendrick test on mice. The article therefore fails to anticipate the claimed invention for the same reason as the Pillemer article.

d. *Hewlett & Wolff, J. BACTERIOLOGY 127:890-98 (1976)*

This article (Gram Aff., Exh. F) is directed to the separation and identification of a soluble adenylate cyclase. It describes a process of extracting adenylate cyclase from exponentially growing *B*. pertussis cells in a tricine buffer and removing the cells by centrifugation.

According to the authors, the resulting protein is "the smallest adenylate cyclase yet recovered," with a molecular weight of approximately 70,000. The adenylate cyclase activity of the protein was determined by measuring its rate of conversion of ATP (adenosine triphosphate) to cAMP (cyclic adenosine monophosphate).

Although this ACAP material would satisfy the claim requirements of the broader claims with respect to

molecular weight and adenylate cyclase activity, there is no disclosure from which it could be inferred that the limitations to "purified" 69k and a proline:glutamic acid ratio of "substantially 1:1" were satisfied.

e. ***Hewlett et al., PROC. NAT'L ACAD. SCI. 73: 1926-30 (1976)***

This publication (Gram Aff., Exh. G) discloses the measurement of adenylate cyclase activity in the extracellular space of *B*. pertussis. The experiments were conducted on a soluble adenylate cyclase with a molecular weight of 70,000, which was produced in accordance with the procedure disclosed in the Hewlett & Wolff article just discussed. As previously stated, there is no suggestion that this material met the claim limitations with respect to purification and proline:glutamic acid ratio.

f. ***Confer & Eaton, SCIENCE 217: 948-50 (1982)***

This article (Gram Aff., Exh. H) reports on an investigation of the effect on phagocytic cells when they are invaded by adenylate cyclase. The adenylate cyclase was extracted from *B*. pertussis cells by treatment with urea and removal of insoluble material by centrifugation. The authors conclude that internalization of the enzyme by phagocytic cells induces unregulated formation of cAMP which suppresses the cells' normal neutrophil and macrophage functions.

Although the ACAP material disclosed in this article might satisfy all of the requirements of the broader patent claims except the limitation to a "purified" antigen, the authors' findings as to its adverse effects on phagocytic cells would appear to contraindicate its use in a vaccine.FN25

FN25. Although defendants have not argued the point, the apparent import of the findings of the authors of this and the Hewlett et al. article is that adenylate cyclase enzymatic activity, and the resulting production of cAMP, is something to be avoided, rather than the "key" to effective immunization as Novotny taught. This may explain why the Takeda vaccine, which has no adenylate cyclase activity, has been so safe as well as so effective.

g. ***Weiss et al., J. INFECTIOUS DISEASES 150: 219-22 (1984)***

This article (Gram Aff., Exh. I) reports the results of a study in which mutant strains of *B*. pertussis were produced in order to determine the manner in which *B*. pertussis causes disease. The study employed supernatant extracts prepared as disclosed in the Confer & Eaton article discussed above. The Weiss et al. article therefore does not anticipate the claimed invention for the reasons previously stated.

h. ***Hewlett et al., DEV. BIOLOGICAL STANDARDIZATION 61: 21-26 (1985)***

This article (Gram Aff., Exh. J) discloses the results of tests to determine the toxic effect of adenylate cyclase in promoting cAMP accumulation in lymphocyte cells. The adenylate cyclase employed was extracted with urea as disclosed in the Confer & Eaton article. The article likewise does not anticipate the claimed invention or teach the preparation of any antigen usable in a vaccine.

i. ***Novotny et al., DEV. BIOLOGICAL STANDARDIZATION 61: 27-41 (1985)*** FN26

FN26. The parties agree that the Novotny article was not in fact published until 1986.

Regardless of whether the priority date of the parent U.S. application is May 12, 1984 or May 1, 1985, this article was published after the latter date and thus does not constitute prior art as a matter of law.

IV. *MOTIONS IN LIMINE*

In light of the foregoing, defendants' motions *in limine* to exclude certain testimony of Gerald Bjorge and Tom Bozzo, and plaintiffs' motions *in limine* to exclude the testimony of Dr. Alison Weiss and evidence regarding a related U.K. litigation, are denied as moot. *See* Harriscom Svenska, AB v. Harris Corp., 3 F.3d 576, 581 (2d Cir.1993) (motions *in limine* are moot where court grants summary judgment).

V. *OTHER MOTIONS*

As indicated above, at the present time the Court need not rule on plaintiffs' motion to correct the patents in suit by adding Montaraz as a co-inventor. Likewise, at present the Court need not decide plaintiffs' motion to compel the return of certain inadvertently produced documents. At oral argument, counsel for plaintiff SmithKline indicated that in making that motion, his client was principally interested in preventing defendants from using the documents at trial, rather than in their physical return. (*See* Tr. at 198-99.) Given that this opinion obviates the need for a trial, the Court will not presently decide that motion.

CONCLUSION

The Court fully appreciates the enormous importance of acellular vaccines capable of providing safe and effective immunity against the scourge of whooping cough which, without such protection, would take the lives of hundreds of thousands of children each year. And the Court does not mean to depreciate the contributions made by Novotny and many others toward the development of such acellular vaccines. But the record clearly reveals that Novotny, although he was apparently able to produce an effective and safe antigen, originally misunderstood both its composition and the reasons for its success. When he filed his original U.K. specification, he identified adenylate cyclase as the "key" antigen "necessary" for effective immunization against *B*. pertussis. Before he filed the parent U.S. application a year later, he had learned from others that he was mistaken, and in that application he identified the "key" antigen merely as a protein having "adenylate cyclase activity," or "ACAP." He was mistaken again. His U.S. specification taught the importance of "purification" of ACAP by substantially removing the other antigenic material which was extracted with it from the outer membrane of *B*. pertussis cells. It now appears that he was mistaken still another time.

The acellular pertussis vaccine which Takeda has been producing and marketing since 1981 is undisputedly effective and safe, has no adenylate cyclase activity and contains a mixture of antigens extracted from the outer membrane of *B*. pertussis cells in which the 69k antigen constitutes only 4% of the total. Medical science has since caught up with Takeda and come to recognize that the most effective pertussis vaccines are those which contain not only 69k but a mixture of at least three antigens. *See* "Pertussis Immunization Update," PEDIATRIC VACCINE REPORTER, Vol. 2, No. 1 (Spring 1998). And apparently the INFANRIX(R) vaccine marketed by plaintiff SmithKline now includes, as its anti-pertussis component, just such a mixture. (*See id*.)

It is undisputed that before Novotny's "discovery" of ACAP, and three years before he filed his first U.K. specification, Takeda's acellular pertussis vaccine was in widespread use in Japan, where it had saved the lives of thousands of children. Takeda had also filed a U.S. patent application disclosing the vaccine and the

method of producing it, and had negotiated with prospective U.S. distributors who promptly began the clinical trials necessary for obtaining FDA approval for sales of the antigen in this country. Indeed, many years before any public disclosure of Novotny's work, the Takeda vaccine was being extensively used here.

At the oral argument of the motions, plaintiffs' counsel dismissed all this history as having become of no consequence when plaintiffs at long last obtained the U.S. patents in suit. But, as the Court has ruled, those patents are not infringed by the Takeda vaccine. Thus, in this case the unyielding technicality of the law need not clash with the popular perception of justice, which would be insulted by compelling defendants to pay tribute to plaintiffs for, or enjoining defendants from, continuing to do what they have been doing commercially for so long without the slightest assistance from Novotny. Indeed, if at the outset Takeda *had* seen Novotny's specification and heeded its teaching that adenylate cyclase activity is necessary for success and that a purified 69k, isolated from and substantially free of other antigens, makes the best vaccine, Takeda would only have been led away from the development of a safe and effective product.

In summary, the Court rules as follows:

(1) Defendants' motion for summary judgment of non-infringement is GRANTED;

(2) Defendants' motion for summary judgment of invalidity for failure to disclose the best mode is DENIED;

(3) Plaintiffs' motion for partial summary judgment that the hybridoma deposit satisfies the best mode requirement is GRANTED;

(4) Defendants' motion for summary judgment of invalidity based on the Takeda prior art is DENIED;

(5) Defendants' motion for summary judgment of invalidity based on the Montaraz et al. article is DENIED;

(6) Plaintiffs' motion for partial summary judgment that none of the claims of the patents in suit, as construed by the Court, is anticipated by any of the other prior art patents or publications discussed above is GRANTED;

(7) Defendants' and plaintiffs' motions *in limine* are DENIED as moot; and

(8) The Court declines to rule at the present time on plaintiffs' motion to correct the patents in suit and their motion to compel the return of certain inadvertently produced documents.

The complaint is dismissed with prejudice. Taxable costs will be assessed against plaintiffs.

SO ORDERED.