EXHIBIT 4

IN THE UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF VIRGINIA
(Alexandria Division)

SMITHKLINE BEECHAM CORPORATION, d/b/a GLAXOSMITHKLINE, SMITHKLINE BEECHAM PLC, and GLAXO GROUP LIMITED, d/b/a GLAXOSMITHKLINE,	:	
Plaintiffs,	:	
v.	:	**Civil Action No. 1:07cv1008**
JON W. DUDAS, in his official capacity as Under Secretary of Commerce for Intellectual Property and Director of the United States Patent and Trademark Office, and	:	
UNITED STATES PATENT AND TRADEMARK OFFICE,	:	
Defendants.	:	

DECLARATION OF SHERRY M. KNOWLES IN SUPPORT OF PLAINTIFFS' MOTION FOR A TEMPORARY RESTRAINING ORDER AND PRELIMINARY INJUNCTION

I, Sherry M. Knowles, hereby declare under penalty of perjury that:

1. I am the Senior Vice President and Global Head of the Corporate Intellectual Property of SmithKline Beecham Corporation d/b/a GlaxoSmithKline, Glaxo Group Limited d/b/a GlaxoSmithKline, and SmithKline Beecham plc, the plaintiffs in the above matter and collectively referred to herein as "GSK."

2. I received my B.S., *cum laude*, with Distinction in Chemistry from Duke University. I received my M.S. in Organic Chemistry from Clemson University. Prior to

attending law school, I spent several years at SmithKline Beecham, now GSK, as a pharmaceutical research chemist where I was part of the development team on albendazole, a drug GSK is now distributing in Africa free of charge to eradicate the debilitating disease of elephantitis. I received my J.D., *magna cum laude*, from the University of Georgia where I was a Benjamin Z. Phillips Scholar and member of Order of the Coif. I am admitted to practice in Georgia, the U.S. Court of Appeals for the Federal Circuit, and before the U.S. Patent and Trademark Office.

3. Before returning to GSK, I led the Biotechnology and Pharmaceutical IP Practice at King & Spalding. I represented companies, foundations and universities in connection with patent prosecution, litigation, and other corporate intellectual property issues relating to pharmaceutical, biotechnology and chemical inventions. I have acted as counsel in U.S. and international patent litigations. I have obtained or assisted in the procurement of a large number of U.S. and foreign patents, almost all of which are in the pharmaceutical and biotechnology fields.

4. As Senior Vice President and Global Head of the Corporate Intellectual Property of GSK, I am familiar with GSK's business, its extensive research and development efforts, the current U.S. patent system, and GSK's prosecution of patent applications under that system. I attend meetings at which decisions are made whether to invest large amounts of capital to take a lead drug through late stage clinical trials to commercialization. One of the factors in the decision whether to proceed with the most expensive part of human clinical trials ("Phase III") is the existence and strength of the patent protection on the drug. I also attend meetings at which decisions are made whether to make investments in fundamental research technology that might lead to suitable drugs for the treatment of life-threatening diseases, and whether to proceed with

early stage human clinical trials ("Phase I and Phase II"). Again, one of the factors considered in making these decisions is a prediction of the existence, strength and term of future patent protection for potential lead candidates.

5. I am familiar with the PTO's Rules of Practice and Procedure, 37 C.F.R. pt. 1, as they are presently constituted. I am also familiar with the PTO's regulations entitled "Changes to Practice for Continued Examination Filings, Patent Applications Containing Patentably Indistinct Claims, and Examination of Claims in Patent Applications," 72 Fed. Reg. 46716, 46716-46843 (Aug. 21, 2007) (to be codified at 37 C.F.R. pt. 1) ("the Final Rules"). The PTO has indicated that it will implement the Final Rules on November 1, 2007.

I. GSK's Business

6. GSK is the second largest pharmaceutical company in the world. It researches, develops, markets, and sells branded prescription and over the counter therapeutics.

7. GSK researches, develops, tests, and markets life-saving medicines that treat some of the worst human diseases, including cancer, cardiovascular disease, respiratory diseases such as asthma and chronic obstructive pulmonary disease, HIV, depression, diabetes, chemotherapy induced nausea, migraine headaches, psychiatric diseases, and Parkinson's disease.

II. GSK Invests Substantially In Researching And Developing New Drugs

8. The FDA has a very rigorous procedure for the approval of therapeutic drug products, which includes lengthy and detailed preclinical and clinical testing. The FDA-required human clinical trials for pharmaceuticals are referred to as "Phase I" (small scale initial toxicity testing), "Phase II" (continued toxicity and small scale efficacy trials), and "Phase III" (large scale efficacy trials). These trials are highly regulated, expensive, and protracted.

9. GSK's drug research requires a large, up-front, totally at-risk investment.

10. GSK's investments in discovering and developing new drugs include many failed drug development efforts. The discovery and development life cycle for a new drug product can last ten years or more.

11. GSK's financial investment to discover and develop a new drug can meet or exceed $1 billion.

12. In 2006, GSK invested $6.4 billion, or approximately $18 million per day on drug research and development.

13. To protect its investments in discovering and developing new drugs, and to insure a return on its investment, GSK depends on patents. GSK relies on patent protection on drug products successfully brought to market to finance their overall investment in research and development.

14. It has been the experience of the pharmaceutical industry that once a drug's patent protection expires, the drug is copied and sold by others who do not incur the billions of dollars in research investments borne by an innovator company like GSK to create new medicines.

15. Without patent protection or with inadequate protection, GSK would not undertake the huge investments in research and development necessary to bring drugs—including drugs that treat the most serious and life-threatening diseases—into widespread use.

III. The Current Patent Application System Has Allowed GSK To Bring Many Important Life-Saving Drugs To Market

16. Under the current patent system and its well-established incentives, GSK has been able to bring many innovative and beneficial drugs to market. For example, in recent years, GSK has brought to the American public Zofran (for alleviating nausea and vomiting associated with chemotherapy and radiotherapy for cancer); Valtrex (for managing herpes simplex and herpes zoster); Advair (for asthma and other airway obstruction disorders); Imitrex (for migraine

headache); Avodart (for enlarged prostate); Epivir, Combivir, and Trizivir (for HIV); and Coreg (for treating mild-to-severe chronic heart failure), to name only a few. After more than ten years of research and development, GSK also recently launched Tykerb in the United States for the treatment of advanced stage and metastatic breast cancer.

17. Patents and the current system of patent application processing were important in allowing GSK and its development partners to make the critical decisions to proceed with the extensive research and development to support these drug approvals. The patents were also important to insure that GSK recovers the significant costs of development and regulatory approval associated with these and other drugs.

IV. GSK Relies On Continuing Applications

18. A primary goal of research and development at GSK is to identify new classes of chemical compounds that, based on laboratory testing, will be useful for treating a human disease. It is customary for GSK to test many chemical compounds before a potential new class is identified. After this typically long and difficult research effort (typically several years or more), GSK normally files patent applications on the discovered class of new drug products at a very early stage, in almost all cases before commencing human clinical trials. The human clinical trials required by the FDA can take up to ten years or more before drug approval. For GSK and other pharmaceutical companies, there are many more failures than successes in human clinical trials, due to rigorous safety and efficacy assessments.

19. At the time GSK files its initial patent applications, GSK may have little idea which drug candidate in the potential drug class will ultimately succeed after the lengthy regulatory process. GSK may also obtain further information on the drug candidate, including how it should be administered, formulated, manufactured and stored, during the detailed trials. Accordingly, GSK often files a first patent application containing a broad disclosure with the

understanding that it will prosecute narrower and/or additional patent claims in continuing applications, based on this further extensive research.

V. The Current Status Of Some Of GSK's Pending Patent Applications

20. Presently, GSK has approximately 100 or more pending applications in which two or more continuing applications have been filed.

21. Presently, GSK has approximately 30 or more pending applications in which two or more continuing applications and a request for continued examination have been filed.

22. GSK currently has several pending applications that have not yet received a first Office Action on the merits and contain more than 5 independent claims or more than 25 total claims. For example, I have identified the following applications as falling into this category: 11/622,623; 11/569,218; 10/561,081; 10/598,464; 10/597,703; 10/568,251; 10/568,029 and 10/561,137.

VI. A Specific Example Of A GSK Patent Application Family

23. A specific example of a family of applications stem from a provisional application 60/186,419 filed March 2, 2000. On March 2, 2001, GSK filed PCT application number PCT/US01/06688, which was published as WO 01/64679. This PCT application entered the United States on August 28, 2002 under the provisions of 35 U.S.C. § 371 as U.S. Patent Application Serial No. 10/220,103.

24. The '103 application issued on June 26, 2007 as U.S. Patent No. 7,235,551. The '551 patent is attached hereto as Exhibit 1. During prosecution of the '551 patent, GSK filed a request for continued examination.

25. GSK filed a first continuation application of the '103 application on December 20, 2006, which is U.S. Patent Application Serial No. 11/613,517.

26. GSK filed a second continuation application of the '103 application, also on December 20, 2006, which is U.S. Patent Application Serial No. 11/613,598.

27. GSK filed a third continuation application on October 11, 2007, which is U.S. Patent Application Serial No. 11/871,039. The '039 application is a continuation of the '517 application. The "Electronic Acknowledgement Receipt" for the '039 application is attached hereto as Exhibit 2.

28. This patent family describes and claims 1,5-disubstituted-3,4-dihydro-1H-pyrimido[4,5-d]pyrimidin-2-one compounds. The work described in this patent family comes out of a long-standing research and development program on inflammation at GSK and its predecessor companies, which started in the 1970s.

29. The compounds of this family are inhibitors of the CSBP/p38 MAP kinase (which in the body activates cytokines, which are mediators of the inflammatory process). It is now firmly established that CSBP/p38 is one of several kinases involved in a stress-response signal transduction pathway, such as that described in Mayer et al., 3 *Drug Discovery Today*, 49, 49-54 (2006). In addition to inhibiting IL-1 and TNF, CSBP/p38 kinase inhibitors also decrease the synthesis of a wide variety of other pro-inflammatory proteins including, IL-6, IL-8, GM-CSF and COX-2.

30. There are many disease states in which excessive or unregulated cytokine production is implicated in exacerbating and/or causing a disease. Thus, by reducing the level of cytokine production, it is now possible to treat the inflammatory component of many human diseases. The discovery of this kinase therefore opens up a new area of research for targeting a multitude of diseases influenced by this cascade. Some of these diseases include rheumatoid arthritis and other arthritic conditions, sepsis, septic shock and toxic shock syndrome, adult

respiratory distress syndrome, asthma, chronic pulmonary inflammatory disease and chronic obstructive pulmonary disease, atherosclerosis, bone resorption diseases such as osteoporosis, inflammatory bowel disease, Crohn's disease, and ulcerative colitis. To date, companies have completed Phase II studies for rheumatoid arthritis and psoriasis in this general area.

31. GSK made a fundamental research breakthrough as the first to have found and isolated the p38 MAP kinase in the early 1990's. GSK holds a number of patents on this kinase. They include U.S. Patent Nos. 5,883,664; 5,871,934; 5,955,366; 5,777,097; 6,361,773; and 5,869,043.

32. Four isoforms of this enzyme have now been found. As with any area of research, large numbers of compounds are made and tested before a few are selected for development in humans. GSK alone has had at least eight compounds in human testing in this research area prior to recent and successful proof of concept testing for the present three in the pipeline.

33. Pharmaceutical companies have now filed large numbers of patents applications over the years covering many diverse potential drug classes for this target GSK first identified, and many compounds have been tested at least initially in humans. GSK has three in development, Vertex appears to have or have had at least two in development, and Takeda, Johnson & Johnson, Boehringer Ingelheim, and Scios each has or has had at least one in development for treating rheumatoid arthritis, angina, psoriasis, Crohn's disease, inflammatory bowel disease, and atherosclerosis.

34. The exemplified GSK patent family discloses yet another potential chemical class of compounds that show activity in this area. As typically done, the patent specification describes a panoply of inventions around the general discovery of this compound class:

- Chemical formulas that describe variations of the class (*see, e.g.*, Formulas (I), (Ia), (II), (IIa), (III), (IIIa), (IV), (IVa), (V), (Va) in Cols. 4-8 of the '551 patent) (sometimes referred to as "genuses" of compounds);

- Numerous subsets of the broad genuses of (i) which highlight preferred embodiments of the invention (*see, e.g.*, Col. 9, line 10 to Col. 22, line 32) (sometimes referred to as "subgenuses" of compounds);

- Specific examples of compounds within the class (*see, e.g.*, Col. 24, lines 1-31, and Tables 1-7) (in this case over 160 specific compounds, sometimes referred to as "species");

- Processes for the manufacture of the compounds (*see, e.g.*, Col. 24, line 32 to Col. 30, line 21);

- Methods of treatment of human diseases with the disclosed compounds (*see, e.g.*, Col. 30, line 23 to Col. 44, line 15); and

- Pharmaceutically acceptable salts of the disclosed compounds (*see* Col. 22, lines 55-62).

35. The '039 application contains claims directed to a process of making compounds of Formula (IV), and a process to make compounds of Formula (C) (used to make compounds of Formula (IV)).

36. The '598 application contains claims directed to chemical intermediate compounds of Formula (A), etc. used to make compounds of Formula (IV).

37. The '517 application contains claims directed to compounds of Formula (IV) and (IVa) and a process for producing compounds of Formula (IV).

38. GSK, however, has yet to file claims on this class of compounds directed to methods to:

- Treat, including prophylaxis, of specific CSBP/p38 kinase-mediated diseases such as: psoriatic arthritis, Reiter's syndrome, gout, traumatic arthritis, rubella arthritis, acute synovitis, rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis and other arthritic conditions, sepsis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, cerebral malaria, meningitis, ischemic and hemorrhagic stroke, neurotrauma/closed head injury, asthma, adult respiratory distress syndrome, chronic pulmonary inflammatory disease, chronic obstructive pulmonary disease, silicosis, pulmonary sarcososis, bone resorption disease,

osteoporosis, restenosis, cardiac and brain and renal reperfusion injury, congestive heart failure, coronary arterial bypass grafting (CABG) surgery, thrombosis, glomerularnephritis, chronic renal failure, diabetes, diabetic retinopathy, macular degeneration, graft vs. host reaction, allograft rejection, inflammatory bowel disease, Crohn's disease, ulcerative colitis, neurodegenrative disease, muscle degeneration, diabetic retinopathy, tumor growth and metastasis, angiogenic disease, influenza induced pneumonia, eczema, contact dermatitis, psoriasis, sunburn, or conjunctivitis.

- Treat the common cold or respiratory viral infection caused by human rhinovirus (HRV), other enteroviruses, coronavirus, influenza virus, parainfluenza virus, respiratory syncytial virus, or adenovirus in a human. The respiratory viral infection which can exacerbate asthma, chronic bronchitis, chronic obstructive pulmonary disease, otitis media, sinusitis, or wherein the respiratory viral infection is associated with a secondary bacterial infection, otitis media, sinusitis, or pneumonia.

- Treat, including prophylaxis, of inflammation enhanced cough in a mammal. This method includes inflammation enhanced cough associated with cough variant asthma, or eosinophilic bronchitis. These disorders may be directed to treating airway-induced inflammation that is secondary to other respiratory disorders such as viral infections that exacerbate asthma (induced by such infections), chronic bronchitis, and chronic obstructive pulmonary disease. A respiratory viral infection treated in conjunction with the smoke related airway inflammation may also be associated with a secondary bacterial infection, such as otitis media, sinusitis, or pneumonia.

- Treat chronic diseases that have an excessive or increased proliferation of vasculature, such as tumor growth and metastasis, atherosclerosis, and certain arthritic conditions. CSBP kinase inhibitors are useful in blocking the angiogenic component of these disease states. Other chronic diseases having an inappropriate angiogenic component are various ocular neovasularizations, such as diabetic retinopathy.

- Treat periodontal disease to control the inflammation associated with cytokine production in such peroral diseases such as gingivitis and periodontitis.

39. GSK has also not yet submitted, among other inventions, an application claiming specific pharmaceutical compositions for particular routes of administration, e.g. inhalation, buccal, topical, systemic administration (oral, intravenous, intraperitoneal and intramuscular), as well as compositions associated with mg/kg amounts.

VII. The Final Rules Bar GSK From Filing Another Application On This Specific Family

40. Under the current patent system, SmithKline Beecham Corporation could file additional continuation applications as needed that claim the benefit of the March 2, 2000 priority date of the Parent Application, to add new claims directed to at least one or more of the yet unclaimed subject matter.

41. Under the Final Rules, however, GSK cannot submit more than two continuing applications without filing a petition and showing that the claims it would seek to present "could not have been" presented earlier. The PTO has indicated it would allow an applicant "one more" continuing application after November 1, 2007 regardless of how many the applicant had already filed so long as the applicant did not file a continuing application between August 21, 2007, the date the Final Rules were published, and November 1, 2007.

42. On October 11, 2007, GSK filed the third continuation application in GSK's exemplary '103 patent application family. Accordingly, as demonstrated in Exhibit 3 hereto, which was obtained from a PTO slide presentation available at http://www.uspto.gov/web/offices/pac/dapp/opla/presentation/clmcontfinalrule.html, under the Final Rules, GSK may not file another continuation application identifying new claims unless it files a petition showing that the claims "could not have been submitted" earlier. More specifically, the lefthand figure on Slide 21 shows the situation with the '551 patent family. The initial application, "I," issued as the '551 patent and GSK filed two continuation applications on December 20, 2006. Thus, under the Final Rules, Slide 21 demonstrates that GSK was not entitled to a third continuation unless it satisfied the PTO's petition and showing requirement.

43. As Slide 34 of Exhibit 3 shows, because GSK filed the '039 application, which is the third application claiming the benefit of the '103 application's filing date, on October 11, 2007, GSK will not be permitted "one more" application after November 1, 2007.

VIII. The Difficult Choice The Final Rules Pose For GSK

44. I have reviewed the file histories of the exemplified GSK patent family, i.e, the application family claiming priority to the '103 patent application. I have concluded that, in this specific case, GSK cannot file a petition with the PTO averring that GSK could not have filed the additional claims earlier without risking a violation of 37 C.F.R. § 10.85 of the PTO's rules of professional conduct. The company cannot file such a petition because, literally, GSK "could have" filed claims earlier. GSK did not do so, however, because it was not required to do so under the current system of patent laws and regulations. Thus, GSK cannot file a petition under Rule 1.78 of the Final Rules in this case. As a result, under the Final Rules, GSK cannot file any additional continuing applications to the '103 patent application family.

IX. GSK Does Not Know How To Comply With The Vague And Incomprehensible Examination Support Document Requirements

45. Under the new Final Rules, GSK is also subjected to a vague and incomprehensible requirement that it submit an examination support document ("ESD") if GSK submits more than five independent claims or twenty-five total claims to fully claim its inventions. The ESD would require, among other things, that GSK provide the PTO with a search that "involves U.S. patents and patent application publications, foreign patent documents, and non-patent literature." 72 Fed. Reg. at 46842. As discussed earlier in paragraph 22, GSK has already identified several pending applications for which an ESD will be required as of November 1, 2007.

46. Up until the PTO enacted the Final Rules, GSK has always acted under the following simple description of U.S. patent law:

> An inventor has a statutory right to a patent unless the invention that is the subject of the application for the patent is not new or obvious. 35 U.S.C. §§ 102, 103.
>
> To obtain a patent, an inventor must file a written application that contains a specification, an oath and one or more claims. 35 U.S.C. §§ 111, 112.

The law also requires that the claims "particularly point[] out and distinctly claim[] the subject matter which the applicant regards as his invention." 35 U.S.C. § 112 ¶ 2. These statutes are the only current restrictions on GSK's claim presentation. By requiring GSK to comply with the Final Rules' vague and incomprehensible ESD requirement, the PTO has erected a barrier to GSK's statutory right to present all of its patent claims, no matter how many.

47. There are over one hundred patent attorneys in the GSK Intellectual Property Department. With the best of intentions to comply with all U.S. laws, I, as GSK's Senior Vice President and Global Head of the Corporate Intellectual Property, do not know how to direct my employees to comply with the new 37 C.F.R. § 1.265 because it is vague. I cannot in good faith determine the boundaries of the law. Section 1.265(b) requires that a patent search be performed that involves U.S. patents, published U.S. patent applications, foreign patent documents and non-patent literature. The regulation does not provide clear instructions on whether the search is limited to electronic searching or also requires manual searching, how many countries must be included, or which libraries GSK must search. For example, I do not know:

- whether GSK must search all foreign patent documents that ever existed in any country;
- whether GSK must manually search patent offices worldwide;
- whether GSK must translate all documents relating to the subject area of the claim to test for relevance;
- which databases the PTO would deem sufficient;

- whether GSK will be held accountable if alternative databases or manual search engines exist and are not used;
- the scope of the requirement that mandates that GSK cite relevant non-patent literature;
- whether GSK must perform manual searches in universities to find relevant literature;
- the meaning of the term "literature" in this regulation; and
- whether there is cost cap or limitation on the financial burden that complying with this requirement will certainly create.

48. Finally, 37 C.F.R. § 1.265(e) does not cure the vagueness of 37 C.F.R. § 1.265(b). Section 1.265(e) states, in essence, that if the PTO determines that an applicant's ESD, including the applicant's search detailed in the ESD, is insufficient, the PTO will notify the applicant and provide the applicant with a two month period in which to cure the PTO's perceived deficiencies. Once these regulations go into effect, the fact that the PTO accepted or did not accept a search constitutes only evidence, not a binding conclusion, that the search was sufficient.

I declare under penalty of perjury that the foregoing is true and correct.

Executed on this 15th day of October, 2007.

/s/
Sherry M. Knowles