UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF VIRGINIA
NORFOLK DIVISION

APOTEX, INC.	)	
	)	
Plaintiff,	)	
	)	Civil Action No. 2:07cv40
v.	)	
	)	
GLAXO GROUP LIMITED, d/b/a GLAXOSMITHKLINE,	)	
	)	
	)	
Defendant.	)	

COMPLAINT FOR DECLARATORY JUDGMENT

The Plaintiff, Apotex, Inc., for its Complaint against the Defendant, Glaxo Group Limited ("Glaxo"), d/b/a GlaxoSmithKline, alleges as follows:

Nature Of The Action

1. Apotex brings—and is entitled by statute to maintain—this action for declaratory judgment of patent non-infringement under, *inter alia*, the federal Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202, and 21 U.S.C. § 355(j)(5)(C)(i), which is part of the Hatch-Waxman Amendments to the Federal Food, Drug, and Cosmetic Act ("FFDCA"), as amended by Title XI of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Pub. L. No. 108-173, 117 Stat. 2066 (2003) ("MMA").

2. This action arises out of, *inter alia*, Apotex's submission of an Abbreviated New Drug Application ("ANDA") to the U.S. Food and Drug Administration ("FDA") seeking approval to market a generic version of Glaxo's brand-name anti-ulcer medication Zantac® Syrup, known generically as ranitidine hydrochloride.

3. Glaxo purports to own U.S. Patent No. 5,068,249 ("the '249 patent"), a true and accurate copy of which is attached to this Complaint as Exhibit A. Upon submission by Glaxo,

the '249 patent was listed in FDA's so-called "Orange Book," a compilation of approved drugs and their patents. As a consequence of such Orange Book listing, Glaxo maintains, and has affirmatively represented to the world, that the '249 patent claims the approved drug, Zantac® Syrup, or a method of using that drug, and that a claim for patent infringement could reasonably be asserted against any generic ANDA applicant, including Apotex, attempting to market a generic ranitidine product before patent expiration. Moreover, Glaxo already has successfully enforced, and continues to enforce, the '249 patent against other companies seeking to market a generic ranitidine product prior to the expiration of the '249 patent.

4. Apotex has designed around the '249 patent with its proposed generic ranitidine product and so, as required by statute, has certified to FDA that Apotex's ANDA product will not infringe the '249 patent and has further notified Glaxo of the legal and factual bases for that certification. Apotex's submission of a so-called "paragraph IV" certification to the '249 patent constitutes an artificial act of patent infringement putting Apotex at considerable risk of being sued by Glaxo both before and after market entry. Indeed, this regulatory submission created the necessary case or controversy and subject matter jurisdiction for Glaxo to sue Apotex for patent infringement. It likewise created the necessary case or controversy for Apotex to file and maintain an action for declaratory judgment of patent non-infringement.

5. Apotex has satisfied all substantive requirements for approval of its ANDA, and is prepared to begin commercial marketing of its competing generic product prior to expiration of the '249 patent. But Apotex's approval has been delayed and Apotex is presently prevented from competing in the ranitidine market by purported generic marketing exclusivity arising out of the '249 patent. Only a declaratory judgment from this Court can alleviate this harm and allow Apotex to obtain approval of its product and compete in the lucrative ranitidine market.

6. Apotex also faces potentially enormous infringement liability if it markets its generic product prior to expiration of the '249 patent. Only a declaratory judgment from this Court can alleviate this harm and allow Apotex to obtain approval of its product and compete in the lucrative ranitidine market free from infringement liability.

7. Apotex also reasonably believes and apprehends that Glaxo intends to sue Apotex for infringement of the '249 patent. Glaxo has already obtained a judgment of infringement against one competing ANDA applicant, and is presently suing another.

8. Accordingly, there is an actual, substantial, and continuing justiciable case and controversy between Apotex and Glaxo regarding the '249 patent, over which this Court can and should exercise jurisdiction and declare the rights of the parties. Apotex is entitled by law to bring and maintain this action for declaratory judgment of patent non-infringement under the Declaratory Judgment Act and the MMA where, as here, Glaxo did not sue Apotex within 45 days of receipt of Apotex's notice of paragraph IV certification to the '249 patent, and Apotex has offered Glaxo an Offer of Confidential Access to Apotex's ANDA for generic ranitidine oral solution.

9. Apotex is entitled to a judicial declaration that the manufacture, sale, offer for sale, use, or importation of Apotex's proposed generic ranitidine product does not and will not infringe the '249 patent. Absent the exercise of jurisdiction by this Court and such declaratory relief, Apotex and the American public will be irreparably harmed by the indefinite delay in the market entry and availability of lower-priced generic ranitidine.

The Parties

10. Plaintiff Apotex, Inc. is a corporation organized and existing under the laws of Canada and having a place of business at 150 Signet Drive, Weston, Ontario, Canada M9L 1T9. Apotex, Inc. develops and manufactures quality, lower-priced generic medicines.

11. On information and belief, Defendant Glaxo Group Limited ("Glaxo"), doing business as GlaxoSmithKline, is a company organized and existing under the laws of England and Wales and having a registered office at Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex, UB6 ONN, Middelesex, England.

Jurisdiction And Venue

12. This action arises under, *inter alia*, the Patent Laws of the United States, 35 U.S.C. §§ 1 *et seq.*; the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202; and the MMA (21 U.S.C. § 355(j)(5)(C)(i) and 35 U.S.C. § 271(e)(5)).

13. This Court has original jurisdiction over the subject matter of this action under 28 U.S.C. §§ 1331 and 1338(a), because it involves substantial claims arising under the United States Patent Act, 35 U.S.C. §§ 1 *et seq.*; under the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202, because it is an actual controversy concerning the patent-in-suit; and under the MMA (21 U.S.C. § 355(j)(5)(C)(i) and 35 U.S.C. § 271(e)(5)), because Congress has directed that district courts maintain and exercise jurisdiction in such cases.

14. There exists a substantial and continuing actual, justiciable case or controversy between Apotex and Glaxo regarding the '249 patent.

15. This Court can and should declare the rights and legal relations of the parties regarding the '249 patent pursuant to, *inter alia*, the Declaratory Judgment Act, 28 U.S.C. §§ 2201, 2202, and the MMA (21 U.S.C. § 355(j)(5)(C)(i) and 35 U.S.C. § 271(e)(5)).

16. Apotex has the statutory right to bring and maintain this declaratory judgment action under 21 U.S.C. § 355(j)(5)(C)(i). This Court can and should exercise its declaratory judgment jurisdiction over Apotex's claims pursuant to 35 U.S.C. § 271(e)(5).

17. On information and belief, this Court has personal jurisdiction over Glaxo because Glaxo conducts substantial business in, and has regular and systematic contact with, this District. On information and belief, this Court also has personal jurisdiction over Glaxo because Glaxo has submitted to the jurisdiction of this Court in prior litigation. On information and belief, this Court also has personal jurisdiction over Glaxo because Glaxo's attorneys and agents that prosecuted the applications leading to the issuance of the patent-in-suit are located within this District.

18. On information and belief, Glaxo purposefully avails itself of the privilege of doing business as GlaxoSmithKline within the Commonwealth of Virginia and in this District.

19. On information and belief, Glaxo maintains such a continuous and systematic contact with the Commonwealth of Virginia and this District by conducting substantial, regular and systematic business therein through the marketing and sales of its pharmaceutical products—including Zantac® Syrup, the purported commercial embodiment of the patent-in-suit—to allow this Court to reasonably exercise personal jurisdiction over Glaxo.

20. Glaxo previously submitted to the jurisdiction of this Court in *Mutual Pharmaceutical Co., Inc. v. Glaxo Group Limited et al.*, No. 03-426, in which Glaxo admitted and conceded that: (a) Glaxo transacts business within the Commonwealth of Virginia; and, (b) Glaxo maintains such a continuous and systematic contact with the Commonwealth of Virginia and this District by conducting substantial, regular and systematic business therein

through the marketing and sales of its pharmaceutical products to allow this Court to reasonably exercise personal jurisdiction over Glaxo.

21. Venue is proper in this District under 28 U.S.C. § 1400(b). Venue is also proper in this District under 28 U.S.C. §§ 1391 because, *inter alia*, Glaxo is subject to personal jurisdiction in this District; and because Glaxo is an alien corporation.

Background

I. Statutory Scheme For Approval Of New And Generic Drugs.

22. The approval of new and generic drugs is governed by the applicable provisions of the FFDCA, 21 U.S.C. §§ 301 *et seq.*, as amended by the Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585 (1984) (commonly known as the "Hatch-Waxman Amendments" or "Hatch-Waxman"), and amended again by the MMA (codified as amended in relevant part at 21 U.S.C. § 355 and 35 U.S.C. § 271).

A. New drugs and patent listing requirements.

23. Before marketing an original new drug (*i.e.*, not a generic drug) in the United States, the FFDCA, as amended by Hatch-Waxman and the MMA, requires that an applicant submit, and that FDA approve, a new drug application ("NDA") under 21 U.S.C. § 355(b). The NDA must include, *inter alia*, technical data on the composition of the drug, the means for manufacturing it, clinical trial results to establish the safety and efficacy of the drug, and labeling relating to the use of the drug for which approval is requested.

24. An NDA applicant is required, within its NDA, to submit information (*e.g.*, the patent number and expiration date) regarding each patent that claims the drug or method of using the drug that is the subject of the NDA and for which a claim of patent infringement could reasonably be asserted if a person not licensed by the patent owner engaged in the manufacture, use, or sale of the drug product. 21 U.S.C. § 355(b)(1); *see also id.* § 355(c)(2).

25. FDA publishes patent information submitted by an NDA-holder in the Patent and Exclusivity Information Addendum of FDA's publication, *Approved Drug Products with Therapeutic Equivalence Evaluations* (commonly known as the "Orange Book").

26. By filing an NDA and submitting a patent for listing in the Orange Book, the NDA-holder/patent owner, by law, necessarily maintains that the listed patent claims the approved NDA drug, or a method of using that drug, and that an infringement suit could reasonably be asserted against anyone who engages in the manufacture, use, or sale of the drug, and, in particular, against any company that is seeking to make a generic bioequivalent of the NDA drug before patent expiration.

27. Thus, the NDA-holder/patent owner necessarily puts all prospective generic ANDA applicants on notice that a suit for infringement can and will be asserted against any ANDA applicant that attempts to seek approval for and market a generic version of the NDA drug before patent expiration.

28. Such conduct by the NDA-holder/patent owner gives rise to a reasonable apprehension on the generic applicant's part that it will face an infringement suit, or the threat of one, if it attempts to seek approval for or to market a generic version of the NDA drug before patent expiration.

B. Generic drugs and patent certification requirements.

29. The FFDCA, as amended by Hatch-Waxman and the MMA, provides for an ANDA approval process that enables generic pharmaceutical manufacturers to obtain regulatory approval of lower-cost generic versions of previously approved brand-name or NDA drugs on an expedited basis, thereby benefiting the U.S. health-care system and American consumers. The ANDA process is a streamlined version of the full NDA procedure and results

in a generic drug product that is normally marketed under the chemical name of the active drug ingredient.

30. An applicant may invoke this procedure for expedited FDA approval of a generic version of an already-approved NDA drug by submitting an ANDA to FDA under 21 U.S.C. § 355(j).

31. Instead of repeating the clinical studies of safety and efficacy conducted for the previously-approved NDA drug, a generic applicant submitting an ANDA is required to establish, among other details, that its proposed generic product is bioequivalent to the already-approved NDA drug (*i.e.*, has no significant difference in rate and extent of absorption) and that it has the same active ingredient, dosage form, dosage strength, route of administration, and labeling (with certain exceptions) as the approved NDA drug. 21 U.S.C. § 355(j)(2)(A).

32. An ANDA applicant also is required to address each patent properly listed in the Orange Book in connection with the approved NDA drug. In particular, Hatch-Waxman requires an ANDA applicant to submit one of four types of patent certifications for each properly listed patent: (I) that the NDA-holder/patent owner has not submitted any patent information to FDA; (II) that the listed patent has expired; (III) that the patent will expire on a future date, and that the generic applicant will not market its product until after the expiration date (commonly referred to as a "paragraph III certification"); or, (IV) that the listed patent is invalid and/or will not be infringed by the manufacture, use, or sale of the generic drug for which the ANDA is submitted (commonly referred to as a "paragraph IV certification"). 21 U.S.C. §§ 355(j)(2)(A)(vii)(I)-(IV). This last type of certification, a paragraph IV certification, signifies that the generic ANDA applicant intends to market its generic product prior to expiration of the subject patent.

33. When an ANDA applicant submits a paragraph IV certification for a listed patent, the generic applicant must notify the NDA-holder/patent owner that it has filed an ANDA to obtain regulatory approval of a generic version of the NDA drug, and that the ANDA contains a paragraph IV certification for a listed patent (indicating that the ANDA applicant intends to market its generic product before expiration of the listed patent). 21 U.S.C. § 355(j)(2)(B). This notice must contain a detailed statement of the factual and legal bases for the ANDA applicant's certification that the listed patent is invalid and/or will not be infringed by the manufacture, use, or sale of the generic applicant's generic drug product. 21 U.S.C. § 355(j)(2)(B)(iv).

34. The submission of a paragraph IV certification has two important consequences.

35. First, a generic applicant that is first to submit an ANDA containing a paragraph IV certification for a listed patent is entitled to 180 days of generic market exclusivity during which no other competing generic drug products may be marketed. 21 U.S.C. § 355(j)(5)(B)(iv). This statutory benefit is commonly known as "180-day exclusivity."

36. In particular, the statutory provision of the FFDCA applicable here provides that "[i]f the application contains a certification described in subclause (IV) of paragraph (2)(A)(vii) and is for a drug for which a previous application has been submitted under this section [containing] such a certification, the application shall be made effective not earlier than one hundred and eighty days after" the earlier of: (a) the first commercial marketing of that ANDA applicant's proposed drug; or, (b) any court decision—whether it involves the first applicant or not—that the particular patent that is the subject of the paragraph IV certification is invalid or not infringed. 21 U.S.C. § 355(j)(5)(B)(iv). Thus, unless a subsequent generic applicant can obtain a court decision of non-infringement and/or invalidity as Congress

intended, the approval of its ANDA can be delayed indefinitely by the purported exclusivity of the first-filer.

37. Second, the submission of a paragraph IV certification for a listed patent constitutes an act of infringement that creates the necessary case or controversy and subject matter jurisdiction to enable an NDA-holder/patent owner to file, and a district court to resolve, an action for patent infringement—before the generic drug is actually made, used, or sold—to determine whether the generic drug, if marketed and sold in accordance with the ANDA, would infringe the relevant patent.

38. The submission of a paragraph IV certification likewise creates the necessary case or controversy and subject matter jurisdiction for an ANDA applicant to file a declaratory judgment action against the NDA-holder/patent owner if the ANDA applicant is not sued within the applicable 45-day period, as set forth below.

39. Upon receiving notice of a paragraph IV certification for a listed patent submitted by an ANDA applicant, the NDA-holder/patent owner may file suit for infringement of the listed patent under 35 U.S.C. § 271(e)(2)(A) within 45 days of receiving such notification. Such a suit automatically delays FDA from issuing final approval of the ANDA for up to thirty (30) months. 21 U.S.C. § 355(j)(5)(B)(iii). An ANDA applicant is statutorily prohibited from seeking a declaratory judgment during the 45-day period in which the NDA-holder/patent owner may bring suit after receiving notification of the ANDA and paragraph IV certification. *Id.*

40. If the NDA-holder/patent owner does not file such a suit, the ANDA applicant can file and maintain a suit for declaratory judgment against the NDA-holder/patent owner to obtain patent certainty. Indeed, as explained below, Congress explicitly mandated that an

ANDA-filer is entitled to maintain a declaratory judgment action when it is not sued. 21 U.S.C. § 355(j)(5)(C).

41. Congress enacted Hatch-Waxman and the ANDA approval process in order to expedite the marketing of lower-priced generic drug products. Congress intended that the generic manufacturing and marketing of a drug should be allowed as soon as it is determined that the particular generic drug does not violate patent rights. Congress also intended that full generic competition would not be delayed indefinitely by the 180-day exclusivity period.

II. Congress Explicitly Mandated That An ANDA-Filer May Bring And Maintain A Declaratory Judgment Action When The Brand Company Does Not Bring An Infringement Action.

42. On December 8, 2003, the MMA was signed into law. Title XI of the MMA, labeled "Access to Affordable Pharmaceuticals," amended provisions of the FFDCA and, in particular, Hatch-Waxman.

43. Under the MMA, an ANDA applicant who has filed a paragraph IV certification is statutorily entitled to institute and maintain an action for declaratory judgment against an NDA-holder/patent owner if: (1) the 45-day period has passed since notice of the paragraph IV certification was received; (2) neither the patent owner nor the NDA-holder/patent owner brought an action for infringement of the patent within the 45-day period; and, (3) the notice of paragraph IV certification contains an Offer of Confidential Access to the ANDA. 21 U.S.C. §§ 355(j)(5)(C)(i)(I)(aa)-(cc).

44. Once these three conditions are met, the MMA specifically and unequivocally provides that an ANDA applicant "may, in accordance with section 2201 of Title 28 [of the United States Code] bring a civil action under such section against the owner or holder referred to in such subclause . . . for a declaratory judgment that the patent is invalid or will not be

infringed by the drug for which the applicant seeks approval . . . ." 21 U.S.C. § 355(j)(5)(C)(i)(II).

45. An ANDA applicant may exercise its right to file and maintain a declaratory judgment action under the MMA regardless of whether or not the Offer of Confidential Access to Application is accepted.

46. The new declaratory judgment provision contained in the MMA, Section 1101 of the MMA, 117 Stat. 2066, 2454-2456, applies to all ANDAs pending on or after December 8, 2003, which includes these proceedings.

47. Congress' intent in amending 21 U.S.C. § 355(j)(5)(C)(i) and 35 U.S.C. § 271(e)(5) was to extend to ANDA applicants, like Apotex here, the right to file and maintain a declaratory judgment action for patent noninfringement and/or invalidity against an NDA-holder/patent owner, and to direct the district court to exercise subject matter jurisdiction in such an action.

48. The purpose of this provision was two-fold. First, Congress enacted the declaratory judgment provision to allow generic applicants to obtain court decisions that would expedite the introduction of generic drugs by allowing the generic applicant to obtain approval of its ANDA and clear up any bottleneck in the market created by another applicant's 180-day exclusivity. Second, Congress intended to allow generic applicants to obtain patent certainty before marketing their generic products in order to avoid potentially catastrophic infringement damages.

III. The '249 Patent-In-Suit.

49. On or about November 26, 1991, the U.S. Patent and Trademark Office issued the '249 patent, entitled "Aqueous Ranitidine Compositions Stabilized With Ethanol," to David. R. Long.

50. On information and belief, Glaxo purports to be the assignee and owner of the '249 patent, the term of which expires on or about November 26, 2008, according to FDA's Orange Book.

51. On information and belief, Glaxo purports and claims to have the right to enforce the '249 patent.

52. On information and belief, Glaxo alleges that the '249 patent covers and claims its brand-name product Zantac® Syrup, which Glaxo, doing business as GlaxoSmithKline, markets and sells throughout the United States, including in this District.

IV. Glaxo's Zantac® Syrup (Ranitidine Hydrochloride).

53. On information and belief, Glaxo, doing business as GlaxoSmithKline, purports to hold and/or have rights to approved NDA No. 19-675 for ranitidine hydrochloride oral syrup, which is sold by Glaxo, doing business as GlaxoSmithKline, throughout the United States and in this District under the brand-name Zantac® Syrup.

54. Zantac® Syrup (Ranitidine Hydrochloride) is indicated for, among other things, the short-term treatment of active duodenal ulcer.

55. FDA approved Zantac® Syrup (Ranitidine Hydrochloride) on December 30, 1988. Today, Zantac® Syrup remains the only ranitidine oral syrup or solution drug product on the United States market. On information and belief, Zantac® Syrup has generated, and continues to generate, substantial revenues for Glaxo (doing business as GlaxoSmithKline) in the United States that exceed many millions of dollars per year.

56. Glaxo submitted information on the '249 patent to FDA for listing in the Orange Book. By virtue of that submission, FDA listed the '249 patent in the Orange Book in connection with the approved NDA for Zantac® Syrup.

57. By listing the '249 patent in the Orange Book, Glaxo maintains, and has affirmatively represented to the world, that the '249 patent claims Zantac® Syrup, or a method of using that drug, and that an infringement suit could reasonably be asserted against any generic ANDA applicant, including Apotex, that attempts to seek approval for, and market, a generic version of Zantac® Syrup before patent expiration.

58. The listing of the '249 patent in the Orange Book alone objectively creates the necessary case or controversy and subject matter jurisdiction for an ANDA-filer to file and maintain a declaratory judgment action if it is not sued by Glaxo within the requisite 45-day period.

V. Apotex's ANDA For Generic Ranitidine Oral Solution.

59. Apotex has submitted an ANDA (No. 77-602) to FDA seeking approval to market Ranitidine Oral Solution USP, 15 mg/mL, a generic version of Zantac® Syrup, for the treatment of the short-term treatment of active duodenal ulcer.

60. Apotex devoted considerable resources researching, developing, and testing of its generic ranitidine product, all toward compiling the information necessary to submit its ANDA No. 77-602 for generic ranitidine oral solution.

61. In its ANDA, as required by statute and FDA regulation, Apotex included a paragraph IV certification to the '249 patent, stating that the '249 patent will not be infringed by the manufacture, use, offer for sale, sale, or importation of Apotex's generic ranitidine oral solution and/or that the '249 patent is invalid. This certification signified that Apotex intends to market and commercialize its generic ranitidine product prior to expiration of the '249 patent.

62. Apotex's ANDA No. 77-602 is substantially complete and was accepted for filing by FDA.

63. Apotex has satisfied all substantive requirements for approval of its ANDA No. 77-602.

64. Apotex intends, and is prepared, to market its generic ranitidine product before expiration of the '249 patent.

65. Despite satisfying all substantive requirements for approval, Apotex's ANDA has not been approved, and Apotex cannot commercially market its generic product and compete in the market, due to another generic applicant's purported 180-day exclusivity. On information and belief, another generic applicant purports and claims to be the first applicant to submit an ANDA for a generic version of Zantac® Syrup. As a consequence, the approval of Apotex's competing ANDA product has been delayed unless and until Apotex can obtain a court decision of non-infringement and/or invalidity of the '249 patent.

66. In accordance with 21 U.S.C. §§ 355(j)(2)(B), Apotex provided Glaxo with notice that it submitted ANDA No. 77-602 and a paragraph IV certification to the '249 patent. This notice included a detailed statement setting forth the factual and legal bases why the '249 patent will not be infringed by the manufacture, use, offer for sale, sale, or importation of Apotex's generic ranitidine tablets.

67. Upon receipt of Apotex's notice of paragraph IV certification to the '249 patent, Glaxo did not sue Apotex within the 45-day period for instituting an infringement suit under 21 U.S.C. § 271(e).

68. On information and belief, Glaxo still intends to assert the '249 patent against Apotex, putting Apotex at risk of potentially catastrophic infringement damages.

69. To date, Glaxo has never stated or represented that Apotex does not infringe the '249 patent, or otherwise provided Apotex with a covenant-not-to-sue as to that patent.

VI. Apotex's Offer Of Confidential Access To Application.

70. Apotex—by letter and as required under 21 U.S.C. § 355(j)(5)(C)—extended to Glaxo an Offer of Confidential Access to Application to access certain information in Apotex's ANDA for ranitidine oral solution.

71. To date, Glaxo has never accepted Apotex's Offer of Confidential Access to Application.

72. By providing this Offer of Confidential Access to Application, and because Glaxo did not sue Apotex within 45 days of receipt of Apotex's notice of paragraph IV certification, Apotex is statutorily entitled to file and maintain a declaratory judgment action against Glaxo under 28 U.S.C. §§ 2201 and 2202, pursuant to 21 U.S.C. § 355(j)(5)(C).

VII. Glaxo's Litigious Conduct And Vigorous Enforcement Of Its Intellectual Property Rights.

73. Glaxo has a long history and orchestrated program of vigorously enforcing its patents against generic applicants, including Apotex.

74. Glaxo has filed dozens of patent infringement actions seeking to prevent companies from marketing competing generic versions of Glaxo's brand-name drugs.

75. For example, on information and belief, Glaxo has sued numerous ANDA-filers for alleged infringement of patents purportedly covering, among others, its brand-name drugs Zantac®, Paxil®, Zofran®, Ceftin®, Imitrex®, Avandia®, Avandamet®, and Lamictal®.

76. Glaxo has previously sued Apotex for alleged infringement of patents purportedly covering its brand-name drugs Zantac®, Paxil®, Zofran®, and Ceftin®.

VIII. Zantac® Syrup Litigation And Glaxo's Enforcement Of The '249 Patent-In-Suit.

77. Glaxo has further demonstrated a willingness and intention to enforce the '249 patent against similarly-situated generic pharmaceutical companies that have filed an ANDA to market generic ranitidine.

78. In particular, Glaxo filed suit against Apotex's competitor Pharmadyne in the United States District Court for the District of Maryland, asserting infringement of the '249 patent against Pharmadyne's ANDA for a generic version of Zantac® Syrup. *See Glaxo Group Limited et al. v. Pharmadyne Corp., et al.*, No. 96-455 (D.Md.) In that litigation, Glaxo obtained a final judgment of infringement against Pharmadyne, together with a permanent injunction enjoining Pharmadyne from commercially marketing its generic product, and delaying FDA approval of Pharmadyne's ANDA, until after expiration of the '249 patent. *See Glaxo Wellcome, Inc. v. Pharmadyne Corp.*, 32 F. Supp. 2d 265 (D.Md. 1998).

79. Glaxo also has filed suit against Apotex's competitor Teva in the United States District Court for the District of Delaware, asserting infringement of the '249 patent against Teva's ANDA for a generic version of Zantac® Syrup. *See Glaxo Group Limited v. Teva Pharmaceuticals USA, Inc. et al.*, No. 96-455 (D.Del.) That litigation is still ongoing.

IX. There Is A Substantial And Continuing Justiciable Controversy Between Apotex And Glaxo Regarding The '249 Patent.

80. By preparing and filing Apotex's ANDA No. 77-602, Apotex has substantially prepared to make, use, import, offer to sell, and sell generic ranitidine oral solution in the United States. Apotex has satisfied all substantive requirements for approval and is prepared to begin commercial marketing of its competing generic product. But Apotex's approval has been delayed indefinitely by the purported 180-day exclusivity of another applicant. Apotex can obtain approval of its generic product and compete in the lucrative generic ranitidine

market only by obtaining a court decision of non-infringement and/or invalidity of the '249 patent. Apotex is suffering substantial harm as a result of its inability to market a competing generic ranitidine product that can be alleviated only by a declaratory judgment from this Court.

81. Apotex also faces potentially enormous infringement liability if it commences marketing before the '249 patent expires. Apotex can alleviate this harm and obtain patent certainty only through a declaratory judgment from this Court.

82. By submitting its ANDA No. 77-602 to engage in the commercial manufacture, use, offer for sale, sale, or importation of generic ranitidine tablets before the expiration of the '249 patent, as well as filing a paragraph IV certification to the '249 patent, Apotex has committed an artificial act of infringement sufficient to create case or controversy jurisdiction under 35 U.S.C. § 271(e)(2) and Article III of the Constitution.

83. By submitting the '249 patent to FDA for listing in the Orange Book, Glaxo has affirmatively represented to the world, and in particular Apotex, that "a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug." *See* 21 U.S.C. § 355(b)(1); *see also id.* § 355(c)(2). In other words, Glaxo necessarily maintains that an infringement claim on the '249 patent could be reasonably asserted against Apotex.

84. Glaxo did not sue Apotex for infringement of the '249 patent within 45 days of receipt of Apotex's notice of paragraph IV certification. In compliance with 21 U.S.C. § 355(j)(5)(C), Apotex granted Glaxo an Offer of Confidential Access to Apotex's ANDA for generic ranitidine oral solution. As such, Apotex is statutorily entitled to institute—and this

Court has constitutional authority to adjudicate—a declaratory judgment action against Glaxo. 35 U.S.C. § 271(e)(5).

85. Glaxo has demonstrated a willingness and, further, an intention to enforce its '249 patent against similarly-situated ranitidine ANDA-filers, and in fact has already successfully enforced that patent.

86. Glaxo's listing of the '249 patent and Apotex's paragraph IV certification to that patent satisfy Article III of the Constitution by creating the necessary case or controversy between Glaxo and Apotex regarding infringement of the '249 patent.

87. Furthermore, based upon, *inter alia*, the listing of the '249 patent and Glaxo's necessary assertion that an infringement claim could be brought against any generic ranitidine applicant; Apotex's ANDA with a paragraph IV certification to the '249 patent and act of infringement; Apotex's intention to market its generic ranitidine product before expiration of the '249 patent; Glaxo's suits against similarly-situated third-parties concerning the '249 patent; Glaxo's pattern of aggressively enforcing its patents against generic applicants, generally, and against Apotex, specifically, there is a continuing case or controversy between Apotex and Glaxo regarding the '249 patent.

88. All of these facts, either alone or in combination, give rise to a substantial and continuing case or controversy under Article III of the Constitution over which this Court has subject matter jurisdiction.

89. Based on these same facts, Apotex is under a reasonable apprehension that Glaxo will sue Apotex alleging infringement of the '249 patent. Such a reasonable apprehension also creates an actual case or controversy of sufficient immediacy and reality to warrant the issuance of a declaratory judgment.

90. Apotex is also statutorily entitled to file and maintain this declaratory judgment action against Glaxo pursuant to the MMA.

91. To avoid legal uncertainty, to obtain approval of its generic ranitidine product, to protect its substantial investment, to protect its anticipated future investments in its manufacturing process for generic ranitidine oral solution, and to open the generic ranitidine oral solution market, Apotex has instituted this action and is entitled to a declaration of the rights of the parties with respect to the '249 patent.

Claim For Relief
(Declaratory Judgment Of Non-Infringement)

92. Apotex asserts and realleges paragraphs 1 through 92 above as if fully set forth herein.

93. There is an actual, substantial, and continuing justiciable case or controversy between Apotex and Glaxo regarding infringement of the '249 patent.

94. The manufacture, sale, offer for sale, use, or importation of Apotex's proposed ranitidine drug product, that is the subject of ANDA No. 77-602, does not and will not infringe (either literally or under the doctrine of equivalents), directly or indirectly (either by inducement or contributorily), any valid or enforceable claim of the '249 patent.

95. Apotex is entitled to a judicial declaration that the manufacture, sale, offer for sale, use, or importation of Apotex's proposed generic ranitidine drug product, that is the subject of ANDA No. 77-602, does not and will not infringe (either literally or under the doctrine of equivalents), directly or indirectly (either by inducement or contributorily), any valid or enforceable claim of the '249 patent.

Prayer For Relief

WHEREFORE, Apotex, Inc. respectfully prays for judgment in its favor and against Glaxo:

(a) Declaring that the manufacture, sale, offer for sale, use, or importation of Apotex's proposed generic ranitidine drug product, that is the subject of ANDA No. 77-602, does not and will not infringe (either literally or under the doctrine of equivalents), directly or indirectly (either by inducement or contributorily), any valid or enforceable claim of the '249 patent; and,

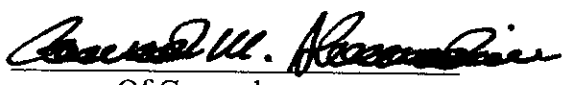
(b) Awarding Apotex its reasonable attorneys' fees and costs of this action; and

(c) Awarding Apotex such other and further relief as the Court may deem just and proper.

Dated: January 24, 2007.

Respectfully submitted,

APOTEX, INC.,

By: 
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United States Patent [19]

Long

[11] Patent Number: 5,068,249

[45] Date of Patent: Nov. 26, 1991

[54] AQUEOUS RANITIDINE COMPOSITIONS STABILIZED WITH ETHANOL

[75] Inventor: David R. Long, Royston, England

[73] Assignee: Glaxo Group Limited, London, England

[21] Appl. No.: 494,804

[22] Filed: Mar. 14, 1990

Related U.S. Application Data

[63] Continuation of Ser. No. 344,620, Apr. 28, 1989, abandoned, which is a continuation of Ser. No. 131,442, Dec. 11, 1987, abandoned.

[30] Foreign Application Priority Data

Dec. 12, 1986 [GB] United Kingdom 86 29781

[51] Int. Cl.[5] A61K 31/34

[52] U.S. Cl. 514/471

[58] Field of Search 514/461, 471

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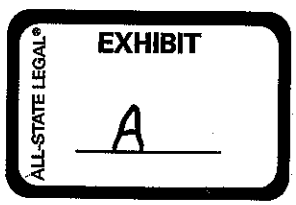
Primary Examiner—Frederick E. Waddell
Assistant Examiner—Diane Gardner
Attorney, Agent, or Firm—Bacon & Thomas

[57] ABSTRACT

The stability of aqueous formulations of ranitidine or a physiologically acceptable salt thereof is enhanced by the addition of ethanol.

12 Claims, No Drawings



AQUEOUS RANITIDINE COMPOSITIONS STABILIZED WITH ETHANOL

This application is a continuation of application Ser. No. 07/344,620, filed Apr. 28, 1989, now abandoned, which is a continuation of Ser. No. 07/131,442, filed Dec. 11, 1987, now abandoned.

The present invention relates to a pharmaceutical composition containing as active ingredient the histamine H_2 antagonist ranitidine.

Ranitidine, [N-[2-[[[5-(dimethylamino)methyl-2-furanyl]methyl]thio]ethyl]-N'-methyl-2-nitro-1,1-ethenediamine, and its physiologically acceptable salts are described in British Patent Specification No. 1565966. In that specification there is reference to liquid formulations for oral and parenteral administrations and there is a description of an aqueous based formulation for intravenous use and another of an oral syrup. Both of these formulations contained sufficient hydrochloric acid to achieve a pH of 5.0 and the syrups also contained Sorbitol solution BPC and a flavour as required.

British Patent Application No. GB 2142820A describes aqueous based formulations containing ranitidine and/or one or more of its physiologically acceptable salts thereof having a pH within the range 6.5–7.5. In that specification there is reference to liquid formulations for oral and parenteral administration and there are examples of aqueous formulations for intravenous and oral use. These formulations contain ranitidine hyrochloride and are buffered to a pH of approximately 7 and for intravenous administration the formulations also contain phenol or sodium chloride. For oral administration the formulation also contains hydroxypropylmethyl cellulose as a viscosity enhancing agent, a preservative (parabens), a sweetening agent and a flavour. These compositions have a significantly greater shelf-life over those in British Patent No. 1565966.

We have now suprisingly found that the stability of ranitidine in aqueous based formulations and more particularly aqueous based formulations for oral administration may be substantially enhanced by the addition of ethanol to the formulation.

Thus the present invention provides a pharmaceutical composition which is an aqueous formulation of ranitidine and/or one or more physiologically acceptable salts thereof also containing ethanol. The aqueous formulation is prepared using ingredients of a purity such that it is suitable for administration to patients and will in general contain at least one conventional pharmaceutical excipient in addition to the ethanol and ranitidine and/or physiologically acceptable salts thereof.

The amount of ethanol present in the formulation is such that the resulting formulation has the enhanced stability. Preferably the amount of ethanol in the composition on a weight/volume basis of the complete formulation, is within the range 2.5% to 10%, and more particularly is between 5 to 10% w/v, more especially 7–8% w/v.

Preferred compositions according to the invention are those in which the pH of the aqueous formulation is within the range 6.5 to 7.5, particularly 6.8 to 7.4 and more especially 7 to 7.3. The required pH of the formulation is preferably obtained by the use of suitable buffer salts for example, potassium dihydrogen orthophosphate and disodium hydrogen orthophosphate or citric acid and disodium hydrogen orthophosphate.

A preferred embodiment of the invention is an aqueous formulation for oral administration. Such a formulation may comprise ranitidine and/or one or more of its physiologically acceptable salts dissolved in water, ethanol, a preservative and a viscosity enhancing agent. Preferably the required pH of the formulation is obtained by the use of appropriate buffer salts. Optionally the composition may also contain other conventional excipients such as a sweetener, a flavour and/or flavouring aids.

Examples of suitable preservatives include on or more alkyl hydroxybenzoates such as methyl, ethyl, propyl and/or butyl hydroxybenzoates.

Examples of suitable viscosity enhancing agents include Xanthan gum, sorbitol glycerol, sucrose or a cellulose derivative such as carboxymethylcellulose or a salt thereof of a C_{1-4} alkyl and/or a hydroxy-C_{2-4}alkyl ether of cellulose such as methylcellulose, ethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxyethylmethylcellulose and hydroxypropylmethylcellulose.

Examples of suitable sweeteners include saccharin sodium, sodium cyclamate, sorbitol and sucrose.

Examples of suitable flavouring agents include 'mint' flavours such as peppermint flavouring agents.

The concentration of ranitidine in the oral formulation, expressed as free base, is conveniently within the range 20–400 mg per 10 ml, for example 20–200 mg per 10 ml, more particularly 150 mg per 10 ml dose.

The amount of ethanol in the formulation for oral administration, expressed as a percentage of the complete formulation on a weight/volume basis, is preferably within the range 2.5 to 10%, and more particularly between 5 to 10%, more especially 7–8%.

The amount of viscosity enhancing agent in the formulation will preferably be sufficient to give a solution with a viscosity in the range of 10 to 100 centipoises.

The aqueous formulations for oral administration are conveniently prepared by mixing an aqueous solution of ranitidine and/or one or more of its physiologically acceptable salts together with ethanol and the excipients, with aqueous solution or dispersion of the viscosity enhancing agent.

The aqueous formulations according to the invention are preferably prepared using ranitidine in the form of its hydrochloride salt.

An illustrative example of a formulation according to the invention is as follows. In this example the relative proportions of ranitidine hydrochloride and the buffer salts are such that the formulation has a pH of approximately 7.

Ranitidine oral liquid formulation (150 mg/10 ml) expressed as free base

	% w/v
Ranitidine hydrochloride	1.68
Ethanol	7.5
Potassium dihydrogen orthophosphate	0.095
Disodium hydrogen orthophosphate anhydrous	0.350
Hydroxypropylmethylcellulose	qs
Preservative	qs
Sweetening agents	qs
Flavour.	qs
Purified water BP to	100 ml

I claim:

1. A pharmaceutical composition which is an aqueous formulation for oral administration of an effective

amount of ranitidine and/or one or more physiologically acceptable salts thereof, said formulation comprising a stabilizing effective amount of ethanol and said composition having a pH in the range of 6.5–7.5.

2. A pharmaceutical composition according to claim 1 containing 2.5% to 10% weight/volume ethanol based on the complete formulation.

3. A pharmaceutical composition according to claim 1 containing 7% to 8% weight/volume ethanol based on the complete formulation.

4. A pharmaceutical composition according to claim 1 having a pH in the range 6.8 to 7.4.

5. A pharmaceutical composition according to claim 1 having a pH in the range 7.0 to 7.3.

6. A pharmaceutical composition according to claim 1 wherein said pH is obtained by the use of buffer salts.

7. A pharmaceutical composition according to claim 1 prepared using ranitidine in the form of the hydrochloride salt.

8. A pharmaceutical composition as claimed in claim 1, wherein the effective amount is 20–400 mg ranitidine per 10 ml dose expressed as free base.

9. A pharmaceutical composition as claimed in claim 1, wherein the effective amount is 20–200 mg ranitidine per 10 ml dose expressed as free base.

10. A pharmaceutical composition as claimed in claim 1, wherein the effective amount is 150 mg ranitidine per 10 ml dose expressed as free base.

11. A pharmaceutical composition which is an aqueous formulation of ranitidine suitable for oral administration containing 150 mg ranitidine per 10 ml dose expressed as free base, said formulation having a pH in the range 7.0 to 7.3 and also containing 7% to 8% weight/volume ethanol based on the complete formulation.

12. A pharmaceutical composition according to claim 11 wherein said pH is obtained by the use of buffer salts.

* * * * *