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Dockets Management Branch
Food and Drug Administration
Room 1061
5630 Fishers Lane
Rockville, MD 20857

Re: Docket No. 01P-0248/00P-0499

The undersigned, on behalf of GlaxoSmithKline Corporation ("GSK"), submits this response to the above-captioned May 16, 2001, citizen petition filed on behalf of the Federal Trade Commission ("FTC"). In that petition, FTC seeks "further guidance" on the requirements for listing of patents in FDA's Approved Drug Products With Therapeutic Equivalence Evaluations ("Orange Book") (Exh. 2) by requesting "clarification" of FDA's response, dated November 21, 2000 (Exh. 1), to a February 3, 2000, citizen petition submitted by Apotex ("the Apotex citizen petition") in relation to the listing of certain GSK patents for its product Paxil®. Each of the issues raised in the FTC petition is directed to the question whether patents claiming one form of an active ingredient are properly listed when the approved drug product contains a different form of the same active ingredient. FTC's inquiries in its citizen petition focus on the listing of certain GSK patents claiming anhydrate forms of paroxetine hydrochloride. Paroxetine hydrochloride is the active ingredient of Paxil®, which contains the hemihydrate form of the active ingredient.

FTC's petition should be denied for the following reasons. First, FDA has already addressed the issues raised in the FTC petition in its response to Apotex's citizen petition, and determined that there was no basis for FDA to delist the patents. This determination is consistent with the governing statute, FDA's own regulations, and relevant case law. Though styled as a request for "clarification," FTC's petition in truth amounts to no more than an unsupported request for reconsideration of FDA's response to the Apotex citizen petition and, indeed, is not a proper citizen petition at all. Tellingly, the parties actually affected by that response – Apotex and the other ANDA filers – have not sought clarification or reconsideration by FDA but instead have commenced court challenges to the listing of GSK's patents. FTC's petition provides no basis for reconsideration of FDA's response.

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Second, FDA's denial of Apotex's citizen petition on the ground that the listing of GSK's patents "complies with the statute and with FDA regulations" is in any event correct: the Hatch-Waxman Act requires the listing of all patents claiming the approved drug, including those patents claiming different crystalline forms of the approved active ingredient. GSK's listing of its patents in the Orange Book is entirely in accord with the relevant statute, regulations, existing case law, and the balance struck by Congress in enacting the Hatch-Waxman Act.

1. **FDA Has Already Adequately Addressed the Issues in FTC's Petition**

Under the FDA's current citizen petition rules, an interested person may file a petition asking FDA "to issue, amend, or revoke a regulation or order, or to take or refrain from taking any other form of administrative action."[1] The agency must respond within 180 days of receipt of the petition, and ultimately must "rule" upon the petition.[2] That ruling is final agency action in the matter, which can then be challenged in court.[3]

Apotex filed its citizen petition on February 3, 2000, and FDA formally responded on November 21, 2000 (Exh. 1). A review of FDA's response makes it clear that FDA has already addressed the issues raised by FTC. No interested party– such as Apotex or another ANDA filer – filed a request for reconsideration or otherwise sought "clarification" by the FDA, but have instead brought their challenges to GSK's patent listings in federal court.[4]

FTC's petition does not meet the requirements of a proper citizen petition. Indeed, that petition does not in fact request any proper agency action at all, but rather amounts to a bare request for an advisory opinion on questions of patent listing under the Hatch-Waxman Act. The questions presented in FTC's petition are fully addressed in the statute and the Agency's implementing regulations, and in the present context FTC's citizen petition is not an appropriate vehicle for re-examining those regulations. In particular, it is not an appropriate vehicle for re-examining FDA's denial of Apotex's citizen petition, given that the interested parties are already before the courts. 21 C.F.R. § 10.33(g) (request for

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1 21 C.F.R. §§ 10.25; 10.30(b).

2 21 C.F.R. § 10.30(e).

3 FDA regulations specifically create and define the administrative record in a petition proceeding for purposes of that review. 21 C.F.R. § 10.30(i).

4 Several actions are pending in the Eastern District of Pennsylvania: SmithKline Beecham Corp. v. Apotex Corp., Civ. No. 99-4304; SmithKline Beecham Corp. v. Geneva Pharmaceuticals, Inc., Civ. No. 99-2926; SmithKline Beecham Corp. v. Zenith Goldline Pharmaceuticals, Inc., Civ. No. 00-1393; SmithKline Beecham Corp. v. AlphaPharm Pty., Ltd., Civ. No. 01-01027. In addition, Apotex has filed a second action in the District of Columbia, Apotex v. Thompson et al., No. 00-729. Each of these actions includes claims challenging GSK's listing of patents in the Orange Book.

reconsideration will be considered only before judicial review action has been brought).[5] This is also the procedure specified by FDA in its response to the Apotex citizen petition, where FDA emphasized that it is patent litigation in the federal courts, not a petition to the agency, that provides the proper avenue for examining GSK's patent listings:

> The statutory 30-month stay on ANDA approvals following initiation of patent litigation affords the opportunity for these potentially challenging issues [of patent validity and scope] to be resolved through the courts. An ANDA applicant sued as a result of its paragraph IV patent certification may certainly raise in that litigation the threshold issue of whether the patent was properly listed in the Orange Book.

(Exh. 1 at 5 (emphasis added)). As FDA reiterated in its recent submission to the United States District Court for the District of Columbia in Apotex's court challenge to GSK's patent listing:

> Congress did not intend FDA to divert its attention from its mission by spending enormous resources attempting to resolve economic disputes about the coverage of patent claims. For this reason, Congress explicitly required FDA to publish patent information upon its submission, and for any such disputes concerning the listing of patents to be resolved by private litigation between interested parties.

FDA Memorandum In Support of Federal Defendants' Motion to Dismiss and in Opposition to Motion for Preliminary Relief, Apotex Inc. v. Thompson et al., No. 1:00CV729 (D.D.C.) (Exh. 3), at 24 (emphasis added).

Each of the interested parties, including Apotex and the other ANDA filers, is before the courts, and the listing issues raised in the FTC petition have been presented to the courts. FDA should defer resolution of these issues to the courts already adjudicating them, and

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[5] One of the primary purposes of recent FDA moves to amend the rules governing citizen petitions was FDA's belief that it was required to address "petitions which simply disagree with an agency decision regardless of the scientific evidence or legal authority supporting that decision." The FDA's proposals also sought to address its concerns with the submission of citizen petitions on the same subject or product. It proposed a formal mechanism for the denial of a "citizen petition that is substantially similar or identical, in terms of its requests and issues, to an earlier administrative proceeding or action, and the citizen petition has not identified any significant change in evidence, laws, or regulations that affect the previous administrative proceeding or action." 64 Fed. Reg. 66822, 66823-24 (November 30, 1999).

should not reopen issues already pending there, in defiance of FDA's own clear instructions and regulations.

2. FDA's Response to the Apotex Citizen Petition is Correct and the GSK Patents are Properly Listed

Moreover, even if FDA were to consider FTC's petition on the merits, it should nonetheless maintain its current position that the GSK patent listing "complies with the statute and with FDA regulations" (Exh. 1 at 5) and reject the assertions set forth in FTC's petition. As noted above, each of FTC's assertions is premised on the erroneous assumption that a patent claiming one form of an active ingredient cannot be listed when the approved product contains a different form of the same active ingredient. Here, the relevant active ingredient (i.e., the active ingredient of Paxil®) is paroxetine hydrochloride, as noted in the Orange Book and FDA's response to Apotex's citizen petition.

FTC contends that only those patents claiming a single form of paroxetine hydrochloride, namely the hemihydrate form found in Paxil® itself, may be listed. But, contrary to FTC's position, the statute and regulations require the listing of all patents claiming the approved drug, not just those drawn to the particular crystalline form contained in the final dosage form, and FDA is thus clearly correct in concluding, as it did in its response to Apotex, that GSK's listing of patents "complies with the statute and with FDA regulations." (Exh. 1 at 5) As explained below, FTC's arguments to the contrary are without merit.

2.1 The Two-Prong Listing Test and the Definition of "Drug"

FTC is correct when it states that there is a two-prong test for Orange Book listing. Specifically, the Hatch-Waxman Act requires the listing of "any patent which claims the drug for which the applicant submitted the application or which claims a method of using such drug and with respect to which 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." 21 U.S.C. § 355(b)(1). Both prongs thus turn on the meaning of the statutory term "drug" – a term that, as discussed below, clearly encompasses different crystalline forms of the approved active ingredient – and FTC's citation to the second prong of the statutory test no more supports the restrictive listing requirements it seeks than does the first prong.[6]

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[6] Indeed, FTC's reliance on the second prong is wholly misdirected. While the first prong addresses the requirements on the claims of a patent for listing in the Orange Book, the second prong concerns the question of whether the patent could reasonably support an infringement action. For example, the second prong could thus allow an NDA holder to decline to submit patent information if the NDA holder believed that the patent was invalid. The second prong in no way restricts the form of the approved drug that the patent must claim in order to be listed.

While FTC asserts that, in listing patents, "one may only consider the drug product in the form approved by the FDA" (FTC Petition at 4), this assertion depends on a fundamentally flawed interpretation of the statutory term "drug" – which FTC asserts should be interpreted to mean "drug product," defined by FTC as "only that product which is the subject of the NDA as approved by FDA." (Id. at 2, 4) But the statutory term is not so limited.

To the contrary, the term "drug" as used in the statute includes not only drug products, as FTC insists, but also active ingredients and manufacturing components, whether or not they are present in the finished dosage form. See 21 U.S.C. § 321(g)(1); 21 C.F.R. § 210.3(b)(7). See also United States v. Generix Drug Corp., 460 U.S. 453, 458-59 (1983) (the term "drug" is "plainly broad enough" to include both active ingredients and completed drug products). Thus, as the FDA explained in its response to the Apotex citizen petition: "Patents must be listed if they claim the drug substance, or active ingredient of an approved drug product." (Exh. 1 at 6 (emphasis added)) Thus, the statute does not restrict the listing of patents in the Orange Book to patents claiming the approved drug product itself, but also mandates listing of patents that claim the active ingredient of that product (and that, of course, could reasonably be asserted against the unlicensed manufacture, use, or sale of the active ingredient) as well.

2.2 Listing of Patents Claiming an Unapproved Aspect of an Approved Drug

FTC's petition also asserts that "a patent containing only an unapproved component cannot satisfy prong one .... In particular, we understand this to be the case even when the claimed unapproved chemical compound differs only in its water of hydration from an unapproved component." (FTC Petition at 3-4) As discussed above, however, a patent that claims the active ingredient of an approved drug product is properly listed under the Hatch-Waxman Act.

As FDA pointed out in its response to the Apotex citizen petition, FDA has determined that "[a]nhydrous and hydrated entities, as well as the different polymorphs [i.e, different crystalline forms], are considered pharmaceutical equivalents." (Exh. 1 at 6, n.16) Being pharmaceutical equivalents means that the drug products "contain the same active ingredient(s)." (Orange Book (Exh. 2) at xv, vii)

Thus, contrary to FTC's petition, FDA policy holds that the active ingredient in an approved drug product encompasses **all** polymorphs or crystalline forms, including the various anhydrous and hydrated forms. Indeed, any other result would have prevented the ANDA submissions at issue here, as the ANDA filers themselves were required to, and did, certify that the active ingredient of the proposed generic drug products was "the same as" that of the listed drug, see 21 U.S.C. § 355(j)(2)(A)(ii), notwithstanding the fact that the active ingredients are asserted to differ in waters of hydration or crystalline forms from the approved product.

The flawed reasoning in FTC's petition is demonstrated by the facts relevant to the listing of the Paxil® patents. As noted above, the approved drug product is Paxil®, and the active ingredient in Paxil® is paroxetine hydrochloride. This is the active ingredient listed in the labelling approved by FDA as part of GSK's NDA. It is also the active ingredient attributed to Paxil® in the Orange Book. (See Exh. 2 at 3-271) GSK has patents claiming both the hemihydrate and anhydrate forms of paroxetine hydrochloride, and all of these patents therefore claim the approved "drug" – paroxetine hydrochloride – for purposes of Orange Book listing under the Hatch-Waxman Act. As FDA thus correctly noted in rejecting the Apotex citizen petition: "Paroxetine hydrochloride anhydrate and paroxetine hydrochloride hemihydrate are pharmaceutical equivalents and contain the same active ingredient, paroxetine hydrochloride." (Exh. 1 at 6 n.16)

Given FDA's current policy as to the "sameness" of all polymorphs and crystalline forms, including the anhydrate and hemihydrate forms of an active ingredient, there is simply no merit to FTC's assertion that the active ingredient of Paxil® should be defined as a single crystalline form, paroxetine hydrochloride hemihydrate, so as to exclude the listing of patents directed to other crystalline forms, such as paroxetine hydrochloride anhydrate. (See FTC Petition at 3-4) To be sure, GSK's commercial Paxil® product contains paroxetine hydrochloride in the hemihydrate form, while several of GSK's patents are directed to the anhydrate form. But the active ingredient approved by the FDA is "paroxetine hydrochloride" – without limitation – as evidenced, for example, by Paxil®'s FDA-approved labelling and its description in the Orange Book. (Exh. 2 at 3-271) FDA's policy is consistent with the compromise of the Hatch-Waxman Act, which permits a generic manufacturer to piggyback on the pioneer's safety and efficacy data, while protecting the pioneer's ability to vindicate its patent rights prior to approval of the generic drug product.

Moreover, GSK's NDA was not, in fact, limited to a single crystalline form of paroxetine hydrochloride. To the contrary, GSK developed the hemihydrate form during the course of clinical trials involving both the hemihydrate and anhydrate forms. GSK disclosed the use of the alternative crystalline forms in its NDA and included data from clinical trials which had been based on both forms. Thus, FDA's approval of Paxil® is premised on clinical trials involving both the anhydrate and the hemihydrate forms of paroxetine hydrochloride. Accordingly, FTC's present assertion that the active ingredient of the approved drug must be limited to the single crystalline form used in the final commercial product is wholly at odds with the manner in which GSK obtained its approval for Paxil® in the first place.

FTC's petition is also contrary to relevant judicial decisions holding that different crystalline forms of an active ingredient should be treated as the same drug for purposes of Orange Book listing. Thus, in Zenith Laboratories, Inc. v. Abbott Laboratories, No. 96-1661, 1996 U.S. Dist. LEXIS 22567 (D.N.J. Aug. 5, 1996), for example, the court rejected a nearly identical argument to the one presently asserted by FTC. There, Zenith, a generic drug manufacturer, moved to compel an NDA-holder to de-list patents directed to different crystalline forms of the active ingredient of an approved drug product, terazosin

hydrochloride, which was used in the approved drug product in the dihydrate form. Abbott, the NDA-holder, later listed patents claiming terazosin hydrochloride in an anhydrous form. Zenith asserted that the listing was not proper because the patents claimed different crystalline forms of the active ingredient. The court rejected Zenith's argument, relying on the statement in the Orange Book that "anhydrous and hydrated entities are considered pharmaceutical equivalents." Id. at *31-32.[7]

The Zenith decision was subsequently followed in Ben Venue Laboratories, Inc. v. Novartis Pharmaceutical Corp., 10 F. Supp. 2d 446 (D.N.J. 1998). In Ben Venue, the court again approved the listing of a patent on an alternative crystalline form of an active ingredient, even though it did not appear in the finished dosage form. Ben Venue argued, as FTC argues here, that a patent directed to an approved active ingredient cannot be listed in the Orange Book if the finished drug product does not contain the exact crystalline form claimed in the patent. The court rejected Ben Venue's argument as "contrary to the FDA's regulatory interpretation, as well as contrary to common sense." 10 F. Supp. 2dat 456. The court based this determination on the FDA's use of the terms "component," "drug substance," and "active ingredient," requiring those terms to have a consistent meaning throughout the regulations governing the drug approval process. The court concluded: "There can be no serious question that, under 21 C.F.R. § 314.53(b), a 'drug substance' or 'active ingredient' may be a 'component' of a drug product regardless of whether it appears in the same form in the drug product." Id. at 458. On that basis, patents may be properly listed regardless of differences in hydration between what is claimed in the patent and what appears in the specific drug product. The same reasoning demonstrates the correctness of FDA's response to the Apotex citizen petition and the propriety of the GSK patent listings.

FTC addresses neither the Zenith nor the Ben Venue decisions in its citizen petition. Instead, it erroneously cites to an FDA filing in Andrx Pharmaceuticals, Inc. v. Biovail Corp., No. 01-CV-6194-DIMITROULEAS (Exh. 4), as supporting its construction of the listing requirements. However, that case involved a patent on a dosage form consideredby FDA to be different from the approved dosage form, not a patent on an active ingredient that FDA considered to be the same as that found in the innovator product. FDA itself made this distinction between patents claiming different dosage forms and those claiming the same active ingredient in its response to Apotex's petition. (Exh. 1 at 6 n.18; see also Ben Venue, 10 F. Supp. 2d at 454-55) FDA's filing in the Biovail case is fully consistent with that response,[8] and with the requirement that FDA distinguish between different dosage forms of

[7] The court left open the possibility that the generic might prove at trial that the different crystalline forms of the active ingredient were not, in fact, equivalent. Id. at *32. Of course, as explained above, such an approach would be fatal to the generic's ANDA as well, and it is not surprising that the Zenith case subsequently settled.

[8] Indeed, while FDA styled its filing in Biovail a "change in position," the change referred to was Biovail's new acknowledgement that the listed patent did not claim the dosage form as approved. As the text of the filing makes clear, FDA's interpretation of the listing criteria remained unchanged. (Exh. 4 at 2)

the same active ingredient for purposes of deciding whether to accept an ANDA. See 21 U.S.C. § 355(j)(2)(A)(iii).

2.3 Listing of Drug Substance Patents

Finally, FTC's petition asserts, without support, that the FDA policy treating different states of hydration or crystalline forms of an active ingredient as the same, as set forth in FDA's response to the Apotex citizen petition (Exh. 1 at 6, n.16), is relevant only to the issue of whether a product contains the "same active ingredient" for filing an ANDA under the Hatch-Waxman Act, see 21 U.S.C. § 355(j)(2)(A)(ii), but purportedly has no bearing on whether a patent is properly listed under those same provisions, see 21 U.S.C. § 355(b)(1) and (c)(2). FTC cites no support for treating these two related sections of the Act differently, and indeed there is none. To the contrary, the prevailing rule is that different sections of the same statute should be construed consistently. Indeed, the court in Ben Venue emphatically rejected the argument now advanced by FTC:

> It is illogical, indeed, even potentially dangerous, for the FDA to have contradictory understandings of critical terms such as 'drug substance,' 'active ingredient,' and 'component' within its own regulations. In the context of statutory interpretation, the Supreme Court has adopted a presumption that terms are given consistent meanings throughout a statute.

10 F. Supp. 2d at 457.

FTC's position is clearly inconsistent with the Act. While it is true that the requirements for patent listing and for filing an ANDA appear in separate subsections of section 505 of the Act, 21 U.S.C. § 355, both parts turn on the same question– the definition of active ingredient in the approved drug product. There is simply no warrant in the Act to define that active ingredient, as FTC urges, as limited to a single crystalline form for purposes of an NDA-holder's obligation to list patents claiming the active ingredient of the approved drug, and then to expand that definition to all crystalline forms (including different waters of hydration) for purposes of submitting an ANDA for generic drug products having the same active ingredient as the approved drug.

To the contrary, it is inconceivable that Congress meant to permit a generic manufacturer to assert that it is using the same active ingredient for ANDA approval purposes when it seeks to market a generic drug product with a different crystalline form of the approved active ingredient, while denying the pioneer the right to list patents for that same crystalline form of the approved active ingredient. Such a result would unfairly give generic manufacturers such as Apotex the right to piggyback on GSK's safety and efficacy data, while denying GSK the right to enforce its patents prior to marketing of the generic product, and would be directly contrary to the balance struck by Congress in enacting the Hatch-Waxman Act.

3. **Conclusion**

In short, the conclusions reached by FDA in its response to the Apotex citizen petition are clear, unambiguous, and correct. GSK properly listed its patents. There is thus a reasonable basis for the listing, and the FDA has committed no error in accepting the listings for publication and rejecting the Apotex citizen petition. GSK acted in accordance with its statutory duty to list the patents, see 21 U.S.C. § 355(b)(1), (c)(2), and (e), and in accordance with Congress's intent to identify and resolve patent disputes prior to ANDA approval.

For this and the other foregoing reasons, the FTC citizen petition is without merit and should be denied.

Respectfully submitted,

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