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Dockets Management Branch
U.S. Food and Drug Administration (HFA-305)
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CITIZEN PETITION
EXPEDITED RESPONSE REQUESTED

REQUEST FOR IMMEDIATE WITHDRAWAL OF FINAL APPROVAL OF SYNTHON'S NDA NO. 21-299 FOR ASIMIA (PAROXETINE MESYLATE) 10 mg, 20 mg, 30 mg and 40 mg TABLETS

On behalf of TorPharm, Inc. ("TorPharm"), the undersigned submits this Petition under Sections 505(b) and (j) of the Federal Food, Drug and Cosmetic Act ("the Act"), and 21 C.F.R. §§ 10.25(a) and 10.30, to request the Commissioner of Food and Drugs ("FDA" or "the Agency") to immediately withdraw final approval of Synthon Pharmaceuticals, Ltd.'s ("Synthon") New Drug Application ("NDA") No. 21-299 for Asimia (paroxetine mesylate) 10 mg, 20 mg, 30 mg and 40 mg tablets, submitted under Section 505(b)(2) of the Act. Because the issues raised herein are not new to the Agency and have already been the subject of considerable public comment in Docket 99D-4809,[1]

[1] Docket 99D-4809 contains the public comments to FDA's "Guidance for Industry: Applications Covered by Section 505(b)(2), Draft Guidance, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), October 1999" (hereinafter the "1999 Draft Guidance"). (*See, e.g.*,

as well as fully-briefed Citizen Petitions in Dockets 02P-0447 and 01P-0323,[2] and given the potential for prejudice and irreparable injury to TorPharm, TorPharm respectfully requests that the Agency consider this Petition on an expedited basis and provide a final ruling within 14 business days.

A. Action Requested.

TorPharm requests that FDA immediately withdraw final approval of Synthon's NDA No. 21-299 for paroxetine mesylate tablets—at least until the expiration of TorPharm's 180-day exclusivity for paroxetine hydrochloride tablets—on the grounds that:

- Upon information and belief, Synthon has not—as required by Section 505(b)(1)(A)—submitted original "full reports of investigations which have been made to show whether or not [paroxetine mesylate] is safe for use and whether [paroxetine mesylate] is effective in use," but instead has without permission referenced and relied solely on the non-public, proprietary data in GlaxoSmithKline's ("GSK") NDA No. 20-031 for Paxil® (paroxetine hydrochloride);[3]

- FDA has no authority under Section 505(b)(2) to rely on GSK's NDA No. 20-031 for Paxil® (paroxetine hydrochloride) to approve Synthon's NDA No. 21-299 for paroxetine mesylate; and

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Tab F.) The comments challenging and opposing the 1999 Draft Guidance are incorporated by reference herein and expressly made part of TorPharm's present Petition and corresponding Docket.

[2] Docket 02P-0447 concerns the Citizen Petition submitted by Pfizer challenging Dr. Reddy's Section 505(b)(2) application for amlodipine maleate tablets. (*See* Tab G.) Docket 01P-0323 concerns the Citizen Petition submitted by Pfizer and Pharmacia challenging FDA's 1999 Draft Guidance. (*See* Tab H.) These fully-briefed and vetted Petitions are also incorporated by reference herein and expressly made part of TorPharm's present Petition and corresponding Docket.

[3] Throughout this Petition, when we refer to "GSK's NDA No. 20-031" or "GSK's NDA data," we of course mean not only all information submitted to FDA in connection with NDA 20-031 itself, but also all supplements and amendments thereto, all findings and conclusions drawn by FDA based on such data and information, and any other pertinent non-public information that GSK has submitted to FDA regarding paroxetine.

- As such, Synthon's NDA No. 21-299 for paroxetine mesylate must effectively be reviewed and approved by FDA, if at all, as an ANDA under Section 505(j), and accordingly subjected to TorPharm's 180-day exclusivity.

Once again, because these issues are not new to the Agency and have already been the subject of considerable public comment and two fully briefed Citizen Petitions, and because TorPharm stands to suffer significant injury and irreparable harm if Synthon's paroxetine mesylate product is marketed during TorPharm's exclusivity period, TorPharm respectfully requests a written response to this Petition within 14 business days, either granting the relief sought herein or explaining in full the Agency's reasons for refusing to grant such relief. TorPharm will treat a failure by the Agency to respond as a final Agency decision not to withdraw final approval of Synthon's NDA for paroxetine mesylate, and will immediately seek all available administrative and/or legal remedies.

B. Statement Of Grounds.

Introduction

In approving Synthon's purported "paper" NDA for paroxetine mesylate tablets under Section 505(b)(2) of the Act, FDA overlooked three issues, any one of which should have precluded Synthon from receiving final approval.

First, if Synthon—without submitting any original data establishing the safety and efficacy of paroxetine mesylate—has secured final FDA approval by relying on any non-public, proprietary data in GSK's NDA No. 20-031 for paroxetine hydrochloride, without a right of reference from GSK, final Agency approval was improper under the plain language of Section 505(b)(2) of the Act, which does not permit such reliance by FDA or Synthon.

Second, Synthon's reliance on GSK's NDA data for paroxetine hydrochloride would be proper, if at all, *only* in the context of an ANDA under Section 505(j), which is the only part of the Act that expressly permits reliance on data for the "listed drug" to support the application. So if, in fact, Synthon and FDA relied on GSK's NDA data, Synthon's application was allowable *only* as an ANDA and, as such, would be subject to TorPharm's 180-day exclusivity period.

Third, even if FDA were permitted to rely on proprietary data in GSK's NDA for approval of a Section 505(b)(2) application (and it isn't), Synthon's application for paroxetine mesylate could ***only*** rely on such GSK data—for a hydrochloride salt—if FDA now accepts the proposition that different salt forms are "Pharmaceutical Equivalents." But FDA has repeatedly stated that this is not the case, and that salts are to be considered "Pharmaceutical Alternatives." *See, e.g., Approved Drug Products with Therapeutic Equivalence Evaluations* ("the Orange Book"), Preface. If FDA intends to make such a substantive policy change, it cannot do so here absent notice-and-comment rulemaking.

TorPharm takes no position on which of the above three scenarios best describes the nature of the paroxetine mesylate drug product for which Synthon has received final FDA approval, since TorPharm does not have access to the entirety of Synthon's application. However, TorPharm does believe that the submission of a paper NDA under Section 505(b)(2), without original safety and efficacy data, and using only standard ANDA bioequivalence studies, cannot as a matter of law be used to end-run either the rigorous safety and efficacy requirements of an NDA submitted under Section 505(b), or the suitability and exclusivity provisions of an ANDA submitted under Section 505(j). Because Synthon has done one or the other here (or both), final approval of Synthon's paroxetine mesylate product was improper, and should be revoked immediately at least until the expiration of TorPharm's exclusivity period.

Factual Background

Reference Listed Drug: Paxil® (paroxetine hydrochloride)

The reference listed drug ("RLD") at issue is GSK's Paxil® (paroxetine hydrochloride) 10 mg, 20 mg, 30 mg and 40 mg tablets, approved by FDA under NDA No. 20-031 on December 29, 1992, for the treatment of depression. The active or therapeutic moiety in Paxil® (paroxetine hydrochloride) is paroxetine, a well-known selective serotonin reuptake inhibitor.

Upon information and belief, the only form of paroxetine for which full investigations and studies have been conducted to demonstrate safety and efficacy is the hydrochloride salt of paroxetine, or paroxetine hydrochloride. Upon information and belief, *no* such studies have been conducted by GSK, Synthon or any other applicant to demonstrate the safety and efficacy of any other salts of paroxetine, and in particular paroxetine mesylate.

TorPharm's ANDA No. 75-356 For Paroxetine Hydrochloride Tablets

On March 31, 1998, TorPharm submitted, pursuant to Section 505(j) of the Act, ANDA No. 75-356 for paroxetine hydrochloride 10 mg, 20 mg, 30 mg and 40 mg tablets. As expressly permitted by Section 505(j) of the Act, TorPharm's ANDA references GSK's Paxil® (paroxetine hydrochloride) drug product and NDA No. 20-031. With its ANDA, TorPharm submitted the requisite bioequivalence studies demonstrating that TorPharm's paroxetine hydrochloride tablets are bioequivalent to GSK's Paxil® (paroxetine hydrochloride) tablets and therefore will be safe and effective for treating depression.

TorPharm was the first applicant to submit an ANDA for paroxetine, and in particular the first ANDA containing, pursuant to Section 505(j)(2)(A)(vii)(IV), a certification of noninfringement ("Paragraph IV certification") for a patent listed in the Orange Book in connection with Paxil® (paroxetine hydrochloride) and NDA No. 20-031. More specifically, TorPharm's ANDA, as initially submitted, contained a Paragraph IV certification for U.S. Patent No. 4,721,723 ("the '723 patent"), which claims the approved form of the listed drug, and which was then the only patent listed in the Orange Book in connection with Paxil®. TorPharm provided notice of its ANDA and Paragraph IV certification for the '723 patent to GSK. In response, on June 26, 1998, GSK sued TorPharm alleging infringement of the '723 patent under 35 U.S.C. § 271(e)(2).

As the first applicant to challenge a listed patent by submitting a paragraph IV certification, TorPharm is statutorily entitled to a 180-day period of regulatory exclusivity, during which time the Agency may not approve other ANDAs for paroxetine tablets. *See* 7/30/03 Letter of G. Buehler (Tab A); 21 U.S.C. § 355(j)(5)(B)(iv). This powerful exclusivity provision "encourage[s] generic drug makers to incur the potentially substantial litigation costs associated with challenging pioneer drug makers' patents." *Mylan Pharms., Inc. v. Shalala*, 81 F.Supp.2d 30, 33 (D.D.C. 2000). The loss or impairment of such exclusivity is considered irreparable.

On July 30, 2003, FDA finally approved TorPharm's ANDA No. 75-356 for paroxetine hydrochloride 10 mg, 20 mg, 30 mg and 40 mg tablets, concluding that TorPharm's product is safe and effective for use as an antidepressant.

Synthon's 505(b)(2) Application For Paroxetine Mesylate

On July 26, 2000, Synthon purported to invoke a different section of the Act, specifically Section 505(b)(2), which codified FDA's so-called "paper" NDA procedure, "which had permitted an applicant to rely on studies published in the scientific literature" to demonstrate safety and efficacy. *See* 1999 Draft Guidance at 1. In particular, Synthon submitted, purportedly under Section 505(b)(2), NDA No. 21-299 for Asimia (paroxetine mesylate) 10 mg, 20 mg, 30 mg and 40 mg tablets for, *inter alia*, the treatment of depression. With that application, Synthon submitted a Paragraph IV certification for the '723 patent—long after TorPharm's certification to the same patent was submitted. In sum, Synthon sought approval to market a paroxetine salt—paroxetine mesylate—that is not the hydrochloride salt approved under GSK's NDA No. 20-031 for which full investigations of safety and efficacy were submitted to FDA.

Nonetheless, the RLD product referenced in Synthon's paroxetine *mesylate* paper NDA application is GSK's Paxil® (paroxetine *hydrochloride*) tablets. Upon information and belief, however, Synthon has not performed any clinical studies to demonstrate the safety and efficacy of paroxetine mesylate as required by Section 505(b) of the Act. Nor, upon information and belief, has Synthon relied on studies published in the scientific literature to support its paper NDA for paroxetine mesylate. Rather, upon information and belief, Synthon has necessarily relied on the non-public, proprietary data contained in GSK's NDA No. 20-031 for paroxetine hydrochloride to support its claims of safety and efficacy for paroxetine mesylate.

Indeed, Synthon's approved labeling for paroxetine *mesylate* suggests that Synthon has, for the most part, simply duplicated the approved labeling for GSK's paroxetine *hydrochloride* tablets. *Compare* August 6, 2003 Synthon approved labeling (Tab C) *with* Prescribing Information for Paxil® (Tab D). In doing so, Synthon directly relies on all of GSK's non-public, proprietary data and clinical studies for paroxetine hydrochloride. Upon information and belief, the only studies of any kind performed by Synthon were bioequivalence studies on paroxetine mesylate—precisely the same type of bioequivalence studies performed by TorPharm and other ANDA applicants on their respective products under Section 505(j). In reviewing and approving Synthon's application, FDA must also have necessarily relied on all of GSK's NDA data.

Notwithstanding TorPharm's 180-day exclusivity for paroxetine tablets, Synthon received, on or about July 3, 2003, final FDA approval to market a paroxetine mesylate

drug product. FDA approved Synthon's final labeling on August 6, 2003, making the product ready for commercial marketing. Upon information and belief, Synthon intends to launch its paroxetine mesylate product prior to the expiration of TorPharm's 180-day exclusivity on the '723 patent. Moreover, while Synthon's product is not currently AB rated by FDA, it is our understanding that Synthon intends to market its paroxetine mesylate product as a fully substitutable alterative to GSK's Paxil® (paroxetine hydrochloride) tablets and TorPharm's generic paroxetine hydrochloride tablets. *See* Synthon Press Release, dated July 7, 2003 (Tab B).

There is a real and substantial threat that TorPharm, who submitted the first ANDA with a Paragraph IV certification for the '723 patent, as well as other patents listed in the Orange Book, will lose the benefit of the 180-day exclusivity provided by Section 505(j)(5)(B)(iv) due to FDA's unlawful approval of Synthon's paper NDA No. 21-299 for paroxetine mesylate. TorPharm requests expedited consideration of this Petition because Synthon's impending product launch substantially threatens TorPharm and its valuable exclusivity; such approval and FDA's position runs contrary to both the Act and FDA's own regulations; and ultimately may require immediate judicial intervention for resolution.

Analysis

1. Final approval of Synthon's paper NDA No. 21-299 for paroxetine mesylate must be withdrawn because, on information and belief, Synthon has not submitted the required safety and efficacy data necessary for final approval of a Section 505(b)(2) application.

According to FDA, Synthon submitted its application for paroxetine mesylate pursuant to Section 505(b)(2) of the Act—a subsection of Section 505(b) that governs the approval of full NDAs. As such, Synthon was required to submit, *inter alia*, "full reports of investigations which have been made to show whether or not such drug is safe for use and whether such drug is effective in use." 21 U.S.C. § 355(b)(1)(A). On information and belief, however, Synthon has not submitted, and FDA has not reviewed, any original Synthon data demonstrating the safety and efficacy of paroxetine mesylate. Rather, both Synthon and FDA must necessarily have relied on GSK's proprietary, non-public NDA data for paroxetine hydrochloride. But this neither FDA nor Synthon are entitled to do under the plain language of the Act. Final approval of Synthon's application for paroxetine mesylate must therefore be withdrawn.

a. FDA may not, as a matter of law, rely on GSK's non-public, proprietary NDA data for paroxetine hydrochloride to approve Synthon's 505(b)(2) application for paroxetine mesylate.

i. The plain language of the Act does not permit such reliance.

The initial and primary focus in a statutory construction analysis is the plain language of the statute. *See Hughes Aircraft Co. v. Jacobson,* 525 U.S. 432, 438 (1999). Section 505(b)(2) of the Act provides:

> An application submitted under paragraph (1) for a drug for which the investigations described in clause (A) of such paragraph and relied upon by the applicant for approval of the application *were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted*...

21 U.S.C. § 355(b)(2) (emphasis added). This provision does not, on its face, authorize—nor does it create any right of reference for—Synthon to rely on GSK's non-public, proprietary NDA data to support a Section 505(b)(2) application.[4] Nor does it authorize FDA to rely on such data in reviewing or approving Synthon's application. Rather, Section 505(b)(2) simply permits the applicant to submit reports of studies which the applicant did not conduct and for which it has no right of reference—and nothing more.

In other words, Section 505(b)(2) applies only where the applicant has *no* "right of reference or use." If interpreted otherwise, it would nullify the provision altogether, since Section 505(b)(2) plainly applies only where there is no right of reference to begin with. As the Supreme Court itself has acknowledged, Section 505(b)(2) merely permits the submission of a so-called "paper" NDA—which is "an application that relies on

[4] It is well-settled that GSK's NDA data constitutes confidential and proprietary trade secret information. *See, e.g., Serono Labs., Inc. v. Shalala*, 35 F. Supp. 2d 1 (D.D.C. 1999); *Anderson v. Dept. of Health & Human Servs.*, 907 F.2d 936 (10th Cir. 1990); *Hoffmann-LaRoche, Inc. v. Harris*, 484 F. Supp. 58, 60 (D.D.C. 1979)(stating in the context of a paper NDA that "the raw data made available by the pioneer applicant is protected and not available as such either to the duplicate applicant or FDA."); *see also* 18 U.S.C. § 1905; 21 U.S.C. § 331(j) (prohibiting FDA disclosure of trade secret information).

published literature to satisfy the requirement of animal and human studies demonstrating safety and effectiveness." *Eli Lilly and Co. v. Medtronic, Inc.*, 496 U.S. 661, 676 (1990).

Even FDA's own regulations recognize that Section 505(b)(2) does not automatically authorize an applicant to rely on proprietary data from another applicant's NDA. An applicant seeking to rely on data from another NDA must submit "a written statement that authorizes the reference and that is signed by the person who submitted the information." 21 C.F.R. § 314.50(g)(1); *see also* 21 C.F.R. § 314.54(a)(1)(i) (requiring 505(b)(2) applicant to submit information required by 21 C.F.R. § 314.50(g)). Such written authorization would obviously be unnecessary if Section 505(b)(2) authorized such reference. It clearly does not.

Where, as here, "the intent of Congress is clear, that is the end of the matter; for the court, as well as the agency, must give effect to the unambiguously expressed intent of Congress." *See Chevron, U.S.A., Inc. v. Natural Res. Def. Council, Inc.*, 467 U.S. 837, 842-43 (1984); *see also Newman v. Love*, 962 F.2d 1008, 1012 (Fed. Cir. 1992) (court "must reject agency interpretations which conflict with plain words of statutory language"). By its plain language, Section 505(b)(2) does not authorize FDA to rely on GSK's non-public proprietary NDA data for paroxetine hydrochloride to approve Synthon's 505(b)(2) application for paroxetine mesylate.

ii. The legislative history confirms that Section 505(b)(2) merely codified FDA's "paper" NDA policy under which the Agency could *not* rely on non-public, proprietary data from another NDA applicant.

This construction of Section 505(b)(2) is reinforced by its legislative history and underlying purpose. *See Kokoszka v. Belford,* 417 U.S. 642, 650 (1974) (court must give statute "such a construction as will carry into execution the will of the Legislature.") (internal quotations and citation omitted). Here, the legislative history is replete with Congressional references to so-called "paper" NDAs, and makes clear that Section 505(b)(2) did nothing more than codify FDA's old "paper" NDA procedure, under which an applicant could rely on the published scientific literature, but *not* another NDA sponsor's proprietary non-public data.

As the legislative history reports, Section 505(b)(2) was enacted so that "the generic manufacturer may submit scientific reports, instead of clinical trials, to support findings of safety and efficacy." *See* H.R. 98-857, Part I, 98th Cong.2d Sess. 36,

reprinted in 1984 U.S.C.C.A.N. 2647, 2649 (using term "Paper NDA"); *Id.* at 2665 (noting that Section 505(b)(2) addresses the filing of "Paper NDAs"); *see also Burroughs Wellcome Co. v. Bowen*, 630 F. Supp. 787, 789 (E.D.N.C. 1986) (noting that 1984 amendments codified FDA's authority to approve ANDAs under Section 505(j) and "paper" NDAs under Section 505(b)(2)—"A 'paper' NDA is one in which the required safety and effectiveness data are not the result of original testing by the NDA applicant, but rather are obtained from literature reports of testing done by others.")

This paper NDA procedure was explicitly defined in FDA's "Finkel Memorandum" to permit literature-based NDAs that do not rely on the proprietary data in another applicant's NDA. *See* 46 Fed. Reg. 27396 (May 19, 1981) (publishing the July 31, 1978 Memorandum penned by Dr. Marion Finkel). The Finkel Memorandum acknowledges that "no data in an NDA can be utilized to support another NDA without express permission of the original NDA holder." *Id.* FDA's December 1980 Federal Register notice further states that FDA's 505(b)(2) policy, as defined by the Finkel Memorandum, "acknowledges that data in the pioneer NDA cannot . . . be used to support an NDA for a generic version of the pioneer product." 45 Fed. Reg. 82052, 82056 (Dec. 12, 1980).

The courts have similarly concluded that the existing law on paper NDAs did not permit FDA to rely, without permission, on data in an NDA to approve another NDA. *See Am. Critical Care v. Schweiker*, 1981 U.S. Dist. LEXIS 12363, at *1-2 (N.D. Ill. May 13, 1981) (ordering publication of the Finkel Memorandum but prohibiting FDA from permitting applicants to rely on previously approved summary statements without first conducting rulemaking); *Upjohn Mfg. Co. v. Schweiker*, 520 F. Supp. 58, 63 (W.D. Mich. 1981) (noting that under paper NDA policy, FDA must rely on independently published studies to approve a duplicate NDA).[5]

Accordingly, there is nothing in the legislative history to suggest that Congress intended Section 505(b)(2) to modify or alter FDA's existing paper NDA policy and procedure. Quite the contrary, there is every indication that for Section 505(b)(2) applications, Congress merely codified the existing tradition of paper NDAs, calling for

[5] FDA has stated that one rationale for allowing a Section 505(b)(2) applicant to rely on proprietary data for the listed drug would "encourage innovation in drug development without requiring duplicative studies to demonstrate what is already known about a drug." (1999 Draft Guidance at 3.) However, it is TorPharm's understanding that all of SmithKline's clinical studies were conducted with paroxetine ***hydrochloride***, never with a ***mesylate*** salt. Thus, it would appear that there is no duplication of data.

them to only rely on published scientific literature, not proprietary data from another NDA applicant.

b. Synthon has not met the requirements of Section 505(b)(2).

There are no published studies or investigations demonstrating the therapeutic safety and efficacy of paroxetine mesylate, much less the full investigations required by the Act. A recent MEDLINE search only identified one Dutch article that discusses a paroxetine mesylate formulation. *See* "Adverse effects after switching to a different generic form of paroxetine: paroxetine mesylate instead of paroxetine HCl hemihydrate," Ned Tijdschr Geneeskd, 2002 Apr. 27;146(17): 811-2 (Dutch) (Tab E). This analysis involved evaluations of exactly two patients. That is hardly the rigorous safety and efficacy standard to which NDA applicants under Section 505(b)(1) are held.

A comparison between the approved labeling of Synthon's drug product and GSK's drug product reveals that nearly every statement concerning testing conditions and results are identical to GSK's NDA reports. For example, Synthon reports testing conditions that involve the same number of patients, same duration of testing, whether single site or multi-site, the same dosages, *etc.* as GSK. The "results" of its tests are nearly identical right down to the same percentages and same deviations. This suggests that Synthon has not performed any of its own independent studies, or relied upon other reports in the published literature, for paroxetine mesylate, but merely relied on GSK's proprietary NDA data for paroxetine hydrochloride. Because Section 505(b)(2) filings cannot, under the statute and its related legislative history, rely on data submitted in a 505(b)(1) filing, Synthon has failed to support its NDA with the required safety and efficacy data. Synthon's final approval must be withdrawn immediately.

* * *

This issue, and in particular the proper interpretation and application of Section 505(b)(2), has already been fully briefed and exhausted in: (1) Docket 02P-0447, in which Pfizer has challenged Dr. Reddy's Section 505(b)(2) application for amlodipine, and further noted that Synthon's 505(b)(2) application for paroxetine mesylate likely suffers from the same infirmities; and (2) Docket 01P-0323, in which Pfizer and Pharmacia have challenged FDA's 1999 Draft Guidance. TorPharm incorporates those Petitions and arguments by reference herein. FDA's 1999 Draft Guidance on Section 505(b)(2) has also been the subject of considerable public comment in Docket 99D-4809. Moreover, GSK has also questioned FDA's interpretation of Section 505(b)(2),

suggesting that it is not clear that the law permits 505(b)(2) applicants to rely on the proprietary data of NDA-holders without authorization (Tab I at 1 n.1 and, and further stating that toxicology and clinical safety/efficacy studies must be required as part of a 505(b)(2) application so that FDA treats such applications as the "special NDAs they truly are, rather than as an extension of the ANDA process" (*Id.* at 6.) For these reasons, the issues raised in this Petition have been exhausted and are fully ripe and ready for an immediate, final determination by the Agency.

2. Synthon has effectively submitted an ANDA with a Section 505(j)(2)(C) suitability petition to secure final approval of a paroxetine mesylate drug product.

As a mater of law, then, FDA should not have reviewed and approved Synthon's application for paroxetine mesylate under Section 505(b)(2). That application should have been reviewed by FDA, if at all, as an ANDA with a suitability petition under Section 505(j). That is, current FDA regulations, set forth at 21 C.F.R. § 314.54(a)(1)(iii), do not state that FDA will allow the unauthorized use of clinical trials performed using one salt form to establish safety and efficacy of a different salt form. Rather, the proper vehicle to secure FDA approval for a proposed drug product that is legally permitted to rely on GSK's proprietary data is an ANDA under Section 505(j) and supporting regulations, 21 C.F.R. §§ 314.50(g); 314.430; 20.21; and 20.61. Moreover, under Section 505(j)(2)(C), an applicant may submit an ANDA seeking approval for a new drug that has a different active ingredient by submitting a suitability petition to FDA. *See* 21 U.S.C. § 355(j)(2)(C). Such a petition must be approved "unless the Secretary finds ... (ii) that any drug with a different active ingredient may not be adequately evaluated for approval as safe and effective on the basis of the information required to be submitted in an abbreviated application." *Id.*

FDA considers different salts of an active moiety to be different active ingredients. *See* Orange Book, Preface ("Different salts and esters of the same therapeutic moiety are regarded as pharmaceutical alternatives. For the purpose of this publication, such products are not considered to be therapeutically equivalent"). As noted above, however, on information and belief, neither the published literature nor independent testing performed by or on behalf of Synthon discloses that Synthon's paroxetine mesylate product has satisfied FDA's rigorous safety and efficacy standards. In fact, on information and belief, the only testing conducted by Synthon for paroxetine *mesylate* was bioequivalence testing—the same type of testing performed by paroxetine *hydrochloride* ANDA applicants.

This can only mean that FDA has evaluated and reviewed Synthon's paroxetine mesylate product and granted final approval on the basis of FDA's determination that paroxetine ***hydrochloride*** is safe and effective in view of the full investigations in GSK's NDA. However, under such circumstances, Synthon's application was, in effect, an ANDA application with a tacit request that FDA grant approval for a different salt under the terms of Section 505(j)(2)(C).

GSK's NDA data may be referenced *only* via the ANDA route of Section 505(j). Unlike Section 505(b)(2), Section 505(j)(2) expressly states that an ANDA shall contain "information to show that the conditions of use prescribed, recommended, or suggested in the labeling proposed for the new drug ***have been previously approved for a drug listed under paragraph (7)***." 21 U.S.C. § 355(j)(2)(A)(i) (emphasis added). This statutory language, by expressly referencing the ***listed drug***, permits FDA to rely on GSK's proprietary NDA data to facilitate the approval of a generic version of the listed drug. No similar language referencing a listed drug is provided in Section 505(b)(2).

Moreover, the structure of Section 505(b)(2) must be balanced against the structure of 505(j). Because Section 505(j) specifically uses language that permits FDA and applicants to rely on the NDA data, had it been Congress' intent to have paper NDA applicants equally rely on such data, it would have inserted precisely the same language into the paper NDA provision of Section 505(b)(2). But it did not do so. As such, the Agency must assume that Congress purposefully intended to insert specific language into one section and not in another. *See BFP v. Resolution Trust Corp.*, 511 U.S. 531, 537 (1994) ("It is generally presumed that Congress acts intentionally and purposefully when it includes particular language in one section of a statute but omits it in another." (citation omitted)).

The structural differences can also be shown via their overall placement in the Act. Paper NDAs are part of Section 505(b), which sets out the requirements for new drugs. That is, paper NDAs under Section 505(b)(2) are unique types of NDAs that are subject to all the rigors of a full NDA review. ANDAs, on the other hand, reside in Section 505(j) and hence are, by design, not types of NDAs. Congress specifically set forth the requirements of NDAs in Section 505(b) under which no reliance on proprietary data is permitted versus Section 505(j) under which some reliance is permitted. *See, e.g., Public Citizen Health Research Group v. FDA*, 185 F.3d 898 (D.C. Cir. 1999)(in the context of FOIA requests, that FOIA operates differently between INDs and NDAs because they are separate sections referring to different application types.)

In effect, if Synthon is relying on GSK's non-public, proprietary NDA data (as TorPharm suspects), then the proper—and indeed only—vehicle for obtaining FDA approval is through the ANDA route under Section 505(j), because that is the only location in the statute where reference to the listed drug is permitted. In these circumstances, to qualify for any review by FDA, Synthon's application under Section 505(b)(2) must be reclassified and placed into the appropriate statutory category—that of an ANDA submitted under Section 505(j), with perhaps a tacit petition under subparagraph (C). *See* 21 U.S.C. § 355(j)(2)(A)(ii)(III).

TorPharm does not presently know whether Synthon's application, if properly construed as a Section 505(j) ANDA, otherwise satisfies all FDA requirements for final approval.[6] But even if it did, Synthon's application, if properly construed as an ANDA filing (as it must be), would still be subject to TorPharm's 180-day exclusivity period and therefore would not be finally approvable at this time. Either way, then, whether reviewed as a Section 505(b)(2) application (which it isn't) or a Section 505(j) ANDA, final approval of Synthon's NDA for paroxetine mesylate must be immediately withdrawn at least until the expiration of TorPharm's exclusivity period.

3. By approving Synthon's NDA for a mesylate salt of paroxetine by relying on data from the hydrochloride salt, FDA has—without notice-and-comment rulemaking—effectively and improperly changed its regulatory course and determined that different salt forms are no longer "Pharmaceutical Alternatives," but rather "Pharmaceutical Equivalents."

Section 505(b)(2) plainly states that, to the extent data may be relied upon without a right of reference, such data must involve "a drug for which the investigations described in clause (A) of such paragraph and relied upon by the applicant for approval of the application." 21 U.S.C. § 355(b)(2). Under current FDA policy and thinking, different salt forms of a drug are Pharmaceutical Alternatives, not Pharmaceutical Equivalents—they are not, in FDA's view, the "same" drug as a consequence. *See* Orange Book, Preface.

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[6] Notably, GSK has challenged Synthon's use of an abridged approval procedure in Europe on the ground that paroxetine mesylate and paroxetine hydrochloride are not essentially similar. (*See* Tab J.) This is consistent with GSK's position that a 505(b)(2) NDA must contain preclinical toxicology and clinical safety/efficacy studies. (*See* Tab I at 6.)

If GSK's NDA data for paroxetine hydrochloride is deemed, in Synthon's case, to be the investigations of "a drug ... relied upon by the applicant for approval," the data gathered from such investigations can only apply if FDA presumes that the different salt forms are not Pharmaceutical Alternatives, but rather Pharmaceutical Equivalents. However, FDA has already stated that this is not the case, and that safety and efficacy data from the two are not necessarily interchangeable. By approving Synthon's application, FDA has essentially modified this policy and rule for Synthon's paroxetine mesylate product without notice-and-comment rulemaking. Such Agency action was arbitrary and capricious and taken in full contravention of FDA's own regulations and policy.

It may very well be the case, as Synthon suggests, that with paroxetine, the "inactive part of the salt (mesylate or hydrochloride) is separated from the active paroxetine molecule in the gastrointestinal tract, leaving only the active paroxetine molecule to be absorbed into the bloodstream and provide the intended effect." (Tab B, Synthon Press Release, dated July 7, 2003). It may further be the case that for paroxetine, the dissolution rates of either the hydrochloride or mesylate forms are almost identical, leading to no *de facto* difference between mesylate or hydrochloride salts of paroxetine. However, if this is the case, and GSK's proprietary data for paroxetine hydrochloride was relied on to establish safety and efficacy for paroxetine mesylate (as TorPharm suspects), and if different salts *per se* are now presumed by FDA to be therapeutically equivalent, the proper and indeed only route for submitting an application to make paroxetine mesylate was via an ANDA under Section 505(j). Again, under such circumstances, TorPharm's 180-day exclusivity period would preclude the issuance of final FDA approval to Synthon at this time.

4. Synthon's labeling is also misleading.

Synthon's approved labeling, in purporting to explain how clinical investigations were conducted, identifies the active ingredient only sporadically, deleting mention of the mesylate salt and emphasizing the active moiety, paroxetine. Emphasizing that the "efficacy of paroxetine" has been studied as opposed to stating that the "efficacy of paroxetine mesylate" or the "efficacy of paroxetine ***hydrochloride***" has been studied (*see, e.g.,* Tab C, August 6, 2003 Synthon approved labeling, pages 6-9) may be misleading to consumers and their prescribing physicians. Indeed, even though Synthon's drug will not be AB rated, Synthon has indicated in press releases physicians will be able to prescribe the mesylate salt with "confidence" for patients undergoing paroxetine therapy with the

brand product. *See,* Tab B, Synthon Press Release, dated July 7, 2003. Synthon, of course, has no basis on which to make such claims, and certainly no full investigations of safety and efficacy for paroxetine mesylate. Absent a full disclosure that the safety and efficacy of the mesylate salt *per se* have *not* been fully studied as required by Section 505(b) of the Act, Synthon's labeling is, at best, deceptive and misleading.

5. Countervailing views.

TorPharm acknowledges its obligation to present countervailing arguments known to it. 21 C.F.R. § 10.30(b). To that end, TorPharm notes that FDA has proposed a contrary interpretation of Section 505(b)(2) in its 1999 Draft Guidance and that certain public comments in Docket 99D-4809 and briefing in Dockets 02P-0447 and 01P-0323 have embraced that contrary position. However, as already articulated above, to the extent that FDA's guidance and the subject comments interpret Section 505(b)(2) to permit reliance on non-public, proprietary NDA data, the guidance and comments are contrary to the plain language of the Act and its legislative history, and should not—and indeed cannot—be adopted by the Agency here.

6. Conclusion.

TorPharm requests immediate action as its rights are substantially implicated. This Petition has conclusively shown that FDA's action in approving Synthon's Section 505(b)(2) paper NDA for paroxetine mesylate was improper in the first instance under the Act. FDA must accordingly withdraw that final approval immediately, at least until the expiration of TorPharm's 180-day exclusivity.

C. Environmental Impact.

The actions requested by this Petition are subject to categorical exclusion pursuant to 21 C.F.R. § 25.30.

D. Economic Impact.

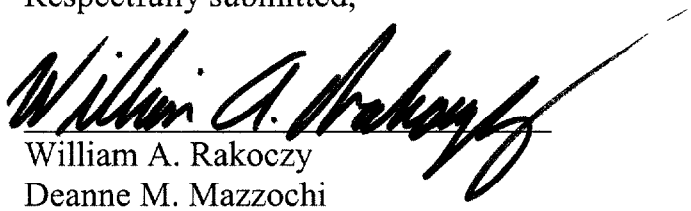
An Economic Impact Statement will be made at the request of the Commissioner.

E. Certification.

The undersigned certify, that, to the best knowledge and belief of the undersigned, this Petition includes all information and views on which the Petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the Petition.

Dated: September 2, 2003.

Respectfully submitted,



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