



November 21, 2000

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BY FEDERAL EXPRESS

Dockets Management Branch
Food and Drug Administration (HFA-305)
5630 Fishers Lane (Room 1061)
Rockville, MD 20852

Re: **Citizen Petition Docket No. 00P-1468/CP1.**

Dear Sir or Madam:

This is submitted on behalf of Pfizer Inc ("Pfizer") in response to the above-captioned citizen petition filed by Lachman Consultant Services, Inc. ("Lachman") on behalf of an unnamed client. In the petition, Lachman asks the Commissioner of Food and Drugs to determine that it is suitable to file an abbreviated new drug application ("ANDA") for sertraline hydrochloride capsules even though the reference drug product, **Zoloft**®, is listed in the Orange Book¹ only in tablet form.² Pfizer holds the approved new drug application ("NDA") for **Zoloft** tablets.

For the reasons below, Pfizer requests that the Commissioner deny the suitability petition.

**The Suitability Petition Should Be Denied Because
It Does Not Meet the Requirements of §505(j)(2)(C)(i).**

1. Food Effect.

Under §505(j)(2)(C)(i) of the Federal Food, Drug, and Cosmetic Act ("the Act"), the Commissioner is required to approve a petition seeking permission to file an ANDA for a drug with a dosage form different from the listed drug unless, among other things, she finds that "investigations must be conducted to show the safety and effectiveness of . . . the dosage form . . ." FDA interprets the "investigations must be conducted" requirement as meaning that "information derived from animal or clinical studies is necessary to show that the drug product is safe or effective". 21 CFR §314.93(e)(2).

The NDA-approved labeling for sertraline tablets reflects data demonstrating that its pharmacokinetics are not meaningfully affected by food. However, without data from Lachman directly on point, sertraline hydrochloride capsules must be presumed to have a

¹ FDA, CDER, "Approved Drug Products with Therapeutic Equivalence Evaluations".

² Lachman's petition covers capsules equivalent to 25 mg, 50 mg, and 100 mg of sertraline hydrochloride based on the 25 mg, 50 mg, and 100 mg reference listed **Zoloft**® tablets.

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potential food effect that may be clinically meaningful and that can vary significantly depending on the formulation of the capsule itself and other factors. This presumption is even reflected in the Orange Book. (See "Therapeutic Equivalence Related Terms"). It defines "therapeutic equivalen[ce]" as requiring, among other things, "pharmaceutical equivalen[ce]", which in turn requires that two drug products have "the same dosage form". In filing its suitability petition, Lachman acknowledged that its client's proposed sertraline capsules are not the same dosage form as the reference listed drug, sertraline tablets.

Pfizer has data on file with FDA that support this straightforward proposition. For example, in one randomized, two-way crossover study³ that assessed plasma concentrations of sertraline following ingestion of a single 100 mg oral capsule under fasting and non-fasting conditions, administration with food statistically significantly increased the oral bioavailability of sertraline as evidenced by an increased peak plasma concentration (C_{max}) of approximately 31.8% and in AUC (0 to 48 hours) by 38.7% but did not affect the time to achieve peak concentration after dosing. Changes of this magnitude are sufficient to cause a test formulation to fail to meet bioequivalence criteria under current standards applied by FDA to ANDAs, let alone to suitability petitions. However, in a second study using a comparable protocol⁴, substantially less pharmacokinetic variability was shown.

The results from these studies demonstrate that there can be wide variability in bioavailability between tablet and capsule formulations of sertraline, as well as among different capsule formulations. The data also show a serious potential for a capsule formulation of sertraline to exhibit clinically significant changes in safety or effectiveness depending on whether it is coadministered with food. And FDA's recently finalized Guidance for Industry on "Bioavailability and Bioequivalence Studies for Orally Administered Drug Products--General Considerations" (October 2000), pp. 17-18, acknowledges the potential clinical relevance of such a food effect. Sertraline is a drug indicated for serious medical conditions, such as depression, where safety and effectiveness are dependent on formulation, correct dosing, and compliance. Lachman's suitability petition provides no information on which the Commissioner might conclude that investigations need not be conducted to demonstrate the safety and effectiveness of sertraline in the specific capsule formulation proposed.

Further, given the potential for significant variability in bioavailability between the reference formulation of sertraline (tablet) and the proposed capsule form, and the dearth of any relevant data or information on this issue in the suitability petition, simple mention in the labeling about the potential food effect would not necessarily be adequate to address these concerns. If Lachman's proposed capsule does show a significant food effect, then the pharmacokinetic differences, particularly when evaluated in a multiple

³ Study 050-216.

⁴ Study 050-024.

dosing study at steady state, may be significant enough to warrant full NDA-type safety or effectiveness studies.

It is clear, then, that because of the wide variability of potential food effect, "investigations must be conducted", within the meaning of §502(j)(2)(C)(i), by Lachman to demonstrate the safety or effectiveness of the particular capsule formulation its client proposes to utilize in the drug product for which ANDA suitability is sought.⁵ Inasmuch as the suitability petition is an exception to the "sameness" requirement otherwise applicable to ANDA's under §505(j)(2)(A), the burden of justifying this statutory exception falls squarely on Lachman (*FTC vs. Morton Salt Co.*, 334 U.S. 37, 44-45 (1948)), who has utterly failed to do so. For these reasons alone, Lachman's petition should be denied and the Commissioner should determine that it is not suitable to file an ANDA for the proposed change in dosage form.

2. Pediatric Testing Under FDA's Pediatric Testing Rule.

Pfizer believes that FDA lacks the legal authority to promulgate its so-called pediatric final rule. See "Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients", 63 Fed. Reg. 66631 (December 2, 1998) ("the Final Rule"). Accordingly, nothing in this submission is intended or should be construed as agreement on Pfizer's part that the agency in fact has such authority nor does it prejudice any rights that Pfizer or others may have. However, assuming *arguendo* that FDA does have the authority claimed, then it must apply the Final Rule evenhandedly, as between a pioneer applicant and an ANDA suitability petitioner.

Equitable application of the Final Rule is compelled by the very justifications FDA relies on in support of the regulation. These were most recently articulated in the agency's denial of a citizen petition seeking revocation of the regulation. Letter, dated November 1, 2000, Docket No. 99P-5215/CP1 ("November 1 Letter"). There, FDA said, among other things, that mandatory pediatric testing ". . . is necessary to provide adequate labeling for the wide range of products that are being used in children without necessary information on pediatric dosing, safety, and effectiveness" (p. 1); "[a]lthough certain costs are associated with the pediatric rule, FDA believes that the rule is necessary to ensure the safe and appropriate use of drugs and biologics in children" (p. 3); ". . . the pediatric rule is necessary because the absence of pediatric information poses significant risks for children" (p. 5); "FDA believes that pediatric patients should receive the same standard of care based upon adequate safety and effectiveness information for pharmaceuticals as adult patients treated with the same drugs for the same labeled

⁵ Nor would it be appropriate, or consistent with FDA practice [see Donald O. Beers, Esq., "Generic and Innovator Drugs, A Guide to FDA Approval Requirements", Fifth Edition (Aspen Law & Business), at p. 3-21 and fn. 79], for the agency to approve the suitability petition on condition that the additional information be submitted as part of the ensuing ANDA.

indications. This **requires** developing pediatric use information and labeling products accordingly". (p. 5 (emphasis supplied)).

Contrary to FDA's own fundamental rationale for the Final Rule, Lachman argues that pediatric investigations should not be required as a condition for approving its ANDA suitability petition. While it admits that its client's proposed drug product will "have pediatric indications in accordance with that of the reference listed drug", Lachman nevertheless maintains that the "pharmacokinetics of Sertraline in the pediatric population have been defined by work of the innovator". It states that the client's product "merely represents a convenience for patients unable to swallow tablets or who prefer capsules." But the discussion above amply demonstrates that a sertraline capsule formulation has substantial potential for pharmacokinetic variability and consequent effect on clinical safety and effectiveness. The proposed change from Pfizer's sertraline tablet to Lachman's sertraline capsule does not represent just a "mere convenience". There is no basis on which to conclude that "the work of the innovator", as reflected in Pfizer's approved NDA and labeling for sertraline tablets, is dispositive of the pharmacokinetics of sertraline capsules in pediatric populations.

In the Final Rule, FDA is clear in requiring that "each application for a . . . new dosage form . . . shall contain data that are adequate to assess the . . . effectiveness of the drug product for the claimed indications in all relevant pediatric subpopulations . . ." 21 CFR §314.55(a). There is nothing in the regulation that can be construed as exempting drugs subject to an ANDA suitability petition from pediatric testing requirements. Indeed, in the Preamble to the final pediatric rule, FDA explicitly addressed how pediatric testing requirements apply in the context of an ANDA suitability petition such as Lachman's:

"[P]etitions submitted under section 505(j)(2)(C) for a change in . . . dosage form . . . may be denied if 'investigations must be conducted' to show the safety and effectiveness of the change. Thus if a petition is submitted for a change that would require a pediatric study under this rule, **the petition must be denied.**"

63 Fed. Reg. 66632, 66640-66641 (December 2, 1998) (emphasis supplied). And FDA recently confirmed this view when it responded to a suitability petition filed by Faulding Pharmaceuticals Co. seeking permission to file an ANDA for a dosage form different from the reference listed drug: "The Agency has determined that your proposed change in dosage form is subject to the Pediatric Rule . . ." Letter, dated April 18, 2000, Docket No. 99P-2252/CP1 (p. 1).⁶

⁶ After determining that the pediatric rule was applicable to Faulding's suitability petition, FDA went on to conclude that a waiver of the requirement was appropriate. But the basis for this waiver, i.e. that "the necessary studies are impossible or highly impractical because the number of such patients is small and geographically dispersed", is inapplicable to sertraline for any of its approved indications.

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Based on the demonstrated pharmacokinetic variability of sertraline capsules (vis à vis the reference tablet and other capsule formulations) and the need to determine whether and to what extent the food effect affects the safety or effectiveness of the drug product that is the subject of the suitability petition, FDA's underlying justification for the pediatric Final Rule is fully applicable in this context. It is clear that, as the term is used in §505(j)(2)(C)(i) of the Act, pediatric "investigations must be conducted" with sertraline capsules. Accordingly, Lachman's suitability petition must be denied.

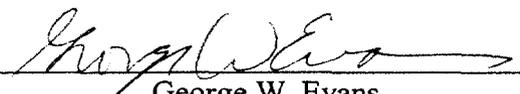
Nor is this harmonization of FDA's pediatric testing regulation with the ANDA suitability petition criteria in §505(j)(2)(C)(i) at odds with the Act, as Faulding claimed in its dialogue with FDA⁷ (and which FDA rejected in any event in its April 18, 2000 letter to Faulding). If, contrary to our view, FDA has the authority to impose the pediatric rule in the first instance, that authority emanates from any number of provisions of the Act relied on by the agency, including §§502(a), 502(f), 505(d)(7), 201(n), 301(a) and (d), 505(A), 502(J), 505(i), 505(k), 701(a), and §351 of the Public Health Service Act. See FDA November 1 Letter at p. 4. Accordingly, the agency is not relegated to §505(j) to determine the scope of its authority over generic drugs in general or suitability petitions in particular as Faulding claims. On the contrary, as the United States Supreme Court has recently taught in **FDA vs. Brown & Williamson Tobacco Corp.**, 529 U.S. _____, _____ (Slip Opinion at p. 9) (2000), "[A] reviewing court should not confine itself to examining a particular statutory provision in isolation. The meaning—or ambiguity—of certain words or phrases may only become evident when placed in context. (citation omitted)." As FDA has already implicitly held, this kind of **Brown & Williamson** analysis of the statute as a whole leads to the inevitable conclusion that if FDA has the authority to promulgate the pediatric rule in the first instance, it clearly has the authority to apply it at least in the context of suitability petitions. This conclusion is especially compelling where, as here, the potential pharmacokinetic variability of sertraline capsules may affect the underlying safety or effectiveness of the drug product.

* * *

For all the foregoing reasons, Pfizer requests that the Commissioner deny approval of Lachman's suitability petition.

Respectfully submitted,

PFIZER INC.

By: 
George W. Evans
Senior Assistant General Counsel

⁷ See e.g. Letter, dated October 7, 1999, to Janet Woodcock, M.D., submitted on behalf of Faulding Pharmaceuticals, Inc.

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cc Gary J. Buehler
Acting Director
Office of Generic Drugs (HFD-600)

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