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February 9, 2001

(OVERNIGHT COURIER 2/9/01)

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

Re: Amendment to Citizen Petition OOP-1468 / CPI

Dear Sir or Madam:

This is submitted in response to the comments submitted by Pfizer Inc. (Pfizer) to the above-referenced petition. Pfizer's letter was dated November 21, 2000. Pfizer's letter requests that the FDA deny approval of the petition requesting permission to file **ah** ANDA for Sertraline Hydrochloride Capsules, a change in dosage form from that of the tablet reference-listed drug product. This amendment addresses the issues raised by Pfizer and provides a regulatory explanation as to the reasons that Pfizer's comments are not applicable to this pending petition.

1. Food Effect

Lachman Consultant Services, Inc. recognizes that the labeling of Sertraline Hydrochloride (Zoloft) Tablets reflects information regarding a potential food effect. Any ANDA submission based on an approved petition for Sertraline Hydrochloride Capsules will be required to submit information to support bioequivalence of the proposed drug product (21 CR 314.94(a)(7)(ii)). As such, an ANDA would be required to contain the results of in-vivo studies, including a fasting, study and a limited food-effect bioequivalence study demonstrating that Sertraline Capsules have a comparable rate and extent of absorption as Zoloft Tablets under both fasting and fed conditions. This type of in-vivo bioequivalence data is the type of information that is routinely required for approval of ANDA drug products that are subject to in-vivo bioequivalence study requirements. If the test and reference products meet the strict bioequivalence requirements imposed by the FDA, they will be considered to have the same therapeutic effect, which eliminates concerns related to a potential for different safety or efficacy profiles.

Bioequivalent drug products are considered to have the same therapeutic effect and thus, have the same clinical effect and safety profile when administered to patients according to the approved labeling. In this case, the FDA would determine whether pharmaceutical alternatives (tablets and capsules) provide the same therapeutic

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effect based on bioequivalence testing of the proposed test and reference products. This testing is expected to include a fasting study and a food-effect bioequivalence study. If the formulation of the ANDA capsule product fails to demonstrate bioequivalence, it cannot be approved as an ANDA. No clinical studies, as suggested by Pfizer, would, therefore, be necessary to demonstrate similar food effects between a tablet and capsule version of the two drug products.

This situation is essentially the same as when an innovator seeks to change dosage forms of its NDA product from a tablet to a capsule or vice versa. Typically, the only requirement for studies would be the same type of bioequivalence studies necessary to assure that the two products had the same rate or extent of absorption. Recent examples of this type of switch include Fluoxetine Hydrochloride Capsules to Tablets and Gabapentin Capsules to Tablets. If the formulation of the ANDA capsule product fails to demonstrate bioequivalence, it simply cannot be approved as an ANDA. This is a review issue associated with a submitted ANDA and not an issue that is germane to deciding whether to approve a petition for a change in dosage form.

For Sertraline Hydrochloride Capsules, safety and efficacy of the drug products may be adequately demonstrated by appropriate bioequivalence and in-vitro testing, which will include results from a food-effect study. Demonstration of biequivalence under appropriate conditions assures that the proposed drug product will have the same rate and extent of absorption and, therefore, can be expected to have the same therapeutic effect, safety and efficacy profile, as the reference-listed drug. As noted above, if the FDA determines that the bioequivalence study data fails to adequately demonstrate bioequivalence, the ANDA will not be approved.

2. Pediatric Testino Under The FDA's Pediatric Testino Rule

Lachman Consultant Services, Inc. agrees with Pfizer's comments regarding the FDA's legal authority to promulgate the pediatric testing rule. Nevertheless, this rule is currently applied to ANDA suitability petitions and was properly addressed in the above-referenced petition.

The regulations (21 CFR 314.55) require submission of pediatric use information. These regulations also include provisions for requesting a Waiver of Submission of studies in pediatric populations. The waiver provisions are addressed in detail in the section entitled Highlights of the Final Rule (Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients; Final Rule). The referenced petition includes a request for a waiver for the need to conduct pediatric studies in accord with the Agency's own regulations.

Based on past actions, the Agency may determine that pediatric studies are required to support approval of a change in dosage form and has denied certain petitions based on its determination that investigations must be conducted in the pediatric population. However, if the Agency determines that a Waiver of Pediatric Study requirements is appropriate, there does not appear to be any regulatory basis to deny the petition solely based on the regulations addressing the requirement for pediatric studies. Therefore, Pfizer's contention that pediatric investigations must be required is in error, as the Agency may decide that the requirement for such studies in this particular instance may be waived.

In summary, the statute permits the FDA to deny petitions submitted pursuant to Section 505(j)(Z)(C) of the act, if investigations must be conducted to show safety or effectiveness of the proposed change requested to the reference-listed drug product. However, if the Agency believes that pediatric studies are not required, and bioequivalence testing comparing the proposed product and the reference- listed drug product is adequate to demonstrate that the products will have the same therapeutic effect (safety and efficacy profile), the Agency must approve the petition. Thus, Pfizer's position that the petition must be denied is not supported by the statute or regulations.

Respectfully submitted,

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