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September 25, 2001

VIA OVERNIGHT MAIL

Dockets Management Branch
5630 Fishers Lane
Room 1061
Mail Stop HFA-305
Rockville, MD 20852

Re: Petition for Stay of Action -- Approval of ANDAs for Cefuroxime Axetil Products Not Containing the Same Active Ingredient as CEFTIN® Products, *i.e.*, Not Containing the Strictly Amorphous Form of the Drug Substance in a Fixed Ratio of R- and S- Isomers (Docket No. 01P-0428/CP)

Dear Sir or Madam:

PETITION FOR STAY OF ACTION

This Petition for Stay of Action is respectfully submitted on behalf of Professional Detailing, Inc. and its wholly-owned affiliate, LifeCycle Ventures (collectively, "PDI"), the exclusive distributor of CEFTIN® Tablets (amorphous cefuroxime axetil) and CEFTIN® for Oral Suspension (amorphous cefuroxime axetil) in the United States.[1]

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1 PDI was granted the exclusive right to market and distribute CEFTIN® in the United States for a period of five years pursuant to a September 2000 agreement with Glaxo Wellcome, now known as GlaxoSmithKline ("GSK"), the manufacturer of CEFTIN®.

01P-0428

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On September 20, 2001, PDI filed a Citizen Petition (Docket No. 01P-0428/CP) asking the Food and Drug Administration ("FDA") to:

> (1) decline to approve any new or pending abbreviated new drug application ("ANDA") or application submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act ("FFDCA") for any generic cefuroxime axetil product in which the cefuroxime axetil does not have the same crystalline structure and stereoisomeric mixture as the cefuroxime axetil in CEFTIN®;
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> (2) stay any approval of the ANDAs filed by Ranbaxy Laboratories, Inc. ("Ranbaxy") and/or Apotex, Inc. ("Apotex") pursuant to 21 U.S.C. § 355(j)(5)(B), in light of the pending patent infringement litigation that GlaxoSmithKline ("GSK"), which holds patents covering CEFTIN®, has commenced against them; and
>
> (3) initiate rulemaking proceedings to set uniform standards for ANDAs in which applicants seek to bypass existing innovator product patents by submitting applications for drugs that contain different crystalline forms and/or stereoisomeric mixtures of active ingredients than are contained in reference listed drugs.

In this Petition, PDI requests that FDA stay the approval of any application and/or decline to approve any new or pending application for a product that includes cefuroxime axetil with a different crystalline structure and/or stereoisomeric mixture than that of CEFTIN® until final resolution of the issues raised in PDI's Citizen Petition.

A. Decision Involved

Presently before the FDA is the question whether the Agency may approve or maintain approval of ANDAs or section 505(b)(2) applications for generic cefuroxime axetil products in which the cefuroxime axetil has a different crystalline structure and/or stereoisomeric mixture than the cefuroxime axetil in CEFTIN®, the FDA-approved reference listed drug. The answer to this question depends on how the Agency addresses the issues raised by PDI's September 20, 2001 Citizen Petition.

B. Action Requested

In this Petition for Stay of Action, PDI requests that FDA stay approval of all new or pending ANDAs or section 505(b)(2) applications for generic products containing cefuroxime axetil that differs in crystalline structure and/or stereoisomeric mixture from the cefuroxime axetil in CEFTIN®. PDI requests that the stay continue until resolution of the issues raised in its Citizen's Petition accepted by the Agency for filing on September 20, 2001. Should FDA deny that Citizen's Petition, PDI asks that the stay requested herein not expire until a reviewing court has ruled on the correctness of that decision so long as PDI seeks court review within two weeks of its receipt of any adverse decision.

Based on publicly available information, PDI understands that at least two ANDAs for generic drug products containing a mixture of crystalline and amorphous cefuroxime axetil are pending at FDA. FDA may be considering approval of at least one such application. Given the necessity for quick review in these circumstances, PDI specifically requests a grant of this Petition for Stay of Action by October 1, 2001. Any failure by the FDA to act on this Petition within that time will, accordingly, constitute the denial of this aspect of the Petition.

C. Statement of Grounds

PDI's Citizen Petition demonstrates that the marketing of generic cefuroxime axetil products in which the drug substance does not have the same crystalline structure and stereoisomeric structure as the active ingredient in CEFTIN® would be contrary to law and could, because of the inherent quality issues, present a risk to the public health. Accordingly, it is crucial that ANDAs for such products not be approved unless FDA has resolved the issues presented by the PDI Citizen's Petition and, if those issues are resolved against PDI, until PDI has an opportunity for judicial review of the Agency decision.

Precedent exists for granting stays where, as here, significant legal and policy issues have been raised about FDA policies. *See*, e.g., 45 Fed. Reg. 82,052 (Dec. 12, 1980) (reference to stay of "paper NDA" policy until 10 days after denial of citizen petition challenging that FDA policy).

This Petition for Stay of Action satisfies the prerequisites for a mandatory grant of a stay under FDA regulations. *See* 21 C.F.R. §10.35(e)(1)-(4).

The petitioner will otherwise suffer irreparable injury. Here, PDI will face diminution of the reputation of its CEFTIN® products if generic products with different quality characteristics are approved and marketed. This injury would be even greater should adverse events result. In addition, PDI will lose sales of its CEFTIN® products once the proposed generic products are marketed. There is no mechanism by which the harm to PDI, if it occurs, can be repaired.

The petitioner's case is not frivolous and is being pursued in good faith. The PDI Citizen's Petition illustrates that PDI's case is not frivolous. It is well grounded in applicable law. This matter is being pursued in good faith. Every attempt is being made to seek resolution in an appropriate and expeditious manner based on the application of relevant law to the facts presented.

The petitioner has demonstrated sound public policy grounds supporting the stay. As FDA is aware, significant clinical experience exists demonstrating that the crystalline structure and stereoisomeric mixture of cefuroxime axetil have a significant impact on the drug's solubility, stability and bioavailability. This fact has been highlighted in the monograph of the United States Pharmacopeia ("USP") (which recently was amended to require that cefuroxime axetil drug products specify the crystalline form of their active ingredient in their labeling), the labeling for CEFTIN®, the former antibiotic monograph for cefuroxime axetil and, indeed, the very approval of CEFTIN®. The only form of cefuroxime axetil that FDA has approved, based on adequate and well-controlled clinical studies demonstrating safety and efficacy, is the strictly amorphous form with a fixed ratio of R- and S-stereoisomers that serves as the active ingredient in CEFTIN®. Permitting the marketing of products containing non-amorphous cefuroxime axetil or different stereoisomeric mixtures would be contrary to governing law. Unless significant testing were performed and tight acceptance criteria adopted and enforced, a crystalline generic could potentially put patients at risk.

This issue is clearly a significant one. Its prompt resolution is important to all concerned. A stay until FDA considers and responds to the PDI Citizen's Petition addressing the questions raised is certainly justified.

The delay resulting from the stay is not outweighed by public health or other public interest. Once the issues presented by the Citizen Petition are addressed by FDA, PDI is confident that FDA will conclude that generic cefuroxime axetil products should be limited to amorphous drug substances with specified stereoisomeric mixtures. There is no public interest in the marketing of inferior products that are not clinically the same as the innovator product. At a time of rising concern about the public health threat posed by the emergence of microbial resistance to antibiotics, the potential for compromised product quality and efficacy is all the more serious -- especially in children, who reflect a major component of the product's primary users. *See* "Proposed Rule: Labeling Requirements for Systemic Antibacterial Drug Products Intended for Human Use," 65 Fed. Reg. 56,511 (Sept. 19, 2000). More generally, there can be no public interest in having FDA pressured into inappropriate approvals by generic product

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sponsors, without considering concerns that are scientifically valid and medically relevant to the propriety of those approvals.

Even were FDA not to find that the criteria for mandatory stay discussed above had been satisfied, such a stay should be granted under the Agency's discretionary authority. FDA is authorized to stay any action "in the public interest and in the interest of justice." 21 C.F.R. §10.35(e). The issues raised by the PDI Citizen's Petition, and by others, are clearly substantial. The interests of the public and of justice demand a fair and timely resolution of those issues in an orderly process.

Fort the reasons stated above, PDI asks that the requested stay be entered as soon as possible and not later than October 1, 2001.

Respectfully submitted,

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