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September 19, 2001

**VIA OVERNIGHT MAIL**

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

**Re: Citizen Petition Regarding Proposed Generic Cefuroxime Axetil Products**

Dear Sir or Madam:

**CITIZEN PETITION**

This Citizen's Petition is submitted on behalf of Professional Detailing, Inc. ("PDI") and its wholly-owned affiliate LifeCycle Ventures ("LCV") (collectively, "PDI"), the exclusive United States distributor and marketer of CEFTIN® Tablets (amorphous cefuroxime axetil tablets) and CEFTIN® for Oral Suspension (amorphous cefuroxime axetil powder for oral suspension). This filing is made under the authority of 21 C.F.R. § 10.30 and sections 505(b) and 505(j) of the Federal Food, Drug and Cosmetic Act (the "FFDCA" or the "Act"), 21 U.S.C. §§ 355(b) and 355(j). We request that the Food and Drug Administration ("FDA") take the following action:

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Washington, DC

*A. Action Requested*

1. Decline to approve any Abbreviated New Drug Application ("ANDA") that seeks approval for a generic cephalosporin antibiotic product containing a mixture of amorphous and crystalline cefuroxime axetil.
2. Decline to approve the pending ANDA submitted by Ranbaxy Laboratories, Inc. ("Ranbaxy"), in which Ranbaxy proposes to market a drug containing a mixture of amorphous and crystalline cefuroxime axetil as a generic substitute for CEFTIN®, which contains wholly amorphous cefuroxime axetil in a fixed ratio of R- and S- stereoisomers.
3. Decline to make effective any approval of the pending ANDA submitted by Ranbaxy or the pending ANDA submitted by Apotex, Inc. ("Apotex") for a generic drug containing a mixture of amorphous and crystalline cefuroxime axetil until either (a) 30 months from the date on which Glaxo Wellcome Inc., now GlaxoSmithKline ("GSK"), commenced a patent infringement action against that applicant; or (b) the date on which a court enters a final order or judgment declaring GSK's U.S. Patent No. 4,562,181 (the "'181 patent") to be invalid and/or not infringed by that applicant's ANDA.
4. Initiate a rulemaking proceeding pursuant to 5 U.S.C. § 553 to set uniform standards for ANDAs in which applicants seek to bypass existing innovator product patents by submitting applications for drugs that contain a different crystalline form and/or different stereoisomeric mixture of an active ingredient that is contained in a reference listed drug.

**B. Statement of Grounds**

**1. Overview**

Several generic drug manufacturers have filed ANDAs seeking approval to market cephalosporin antibiotic tablets containing cefuroxime axetil. These proposed new drugs are combination drugs that contain both crystalline and amorphous cefuroxime axetil as active ingredients. The proposed drugs are *not* the same as CEFTIN® Tablets, the reference listed drug, which has just one active ingredient -- wholly amorphous cefuroxime axetil with a fixed ratio of R- and S- stereoisomers. As set forth herein, the ANDA process is not suitable for review of the proposed new combination drugs, and the pending ANDAs for these drugs cannot be approved, because:

a. The Active Ingredients Are Not the Same. The proposed generic drugs contain active ingredients that are not the "same" as -- *i.e.*, "identical" to -- the active ingredient in CEFTIN®. Specifically, the labeled active ingredient in the approved NDA for CEFTIN® is "cefuroxime axetil in the amorphous form." The proposed generic drugs, by contrast, are combination drugs that contain both amorphous and crystalline cefuroxime axetil as active ingredients. Crystalline cefuroxime axetil clearly is *not* the same as amorphous cefuroxime axetil. On the contrary, crystalline cefuroxime axetil differs substantially from amorphous cefuroxime axetil in its solubility, dissolution, absorption and pharmacokinetics, among other physiological properties. The stereoisomeric mixture of cefuroxime axetil, too, is material to the drug's chemical identity. (CEFTIN® contains amorphous cefuroxime axetil in a fixed ratio of R- and S- isomers.) Both the crystalline structure and the stereoisomeric mixture of any generic versions of CEFTIN® must, therefore, be identical to those of CEFTIN® to merit ANDA approval.

b. ANDA Applicants Cannot Petition to Change CEFTIN®'s Active Ingredient. The ANDA applicants have not petitioned, and cannot petition, to change the active ingredient in CEFTIN®. A petition must be disapproved if it seeks to change an active ingredient in a drug product that was not

classified as a combination drug. CEFTIN® contains only one active ingredient, cefuroxime axetil in the amorphous form, and thus is not a combination drug.

c. The Proposed Generic Drugs Cannot Use the Same Labeling. The amended United States Pharmacopeia ("USP") monograph for cefuroxime axetil, effective September 30, 2001, requires separate label identification to state whether a drug's active ingredient is amorphous cefuroxime axetil, crystalline cefuroxime axetil, or a specific combination of the two. Generic drugs containing a mixture of amorphous and crystalline cefuroxime will be required under USP standards and FDA regulations to include the nature and percentage of both ingredients, and thus will not be able to use the same labeling as CEFTIN®. These generic products must, therefore, be considered new drugs for which an NDA is required.

d. Approval is Bad Public Policy. The proponents of the pending ANDAs have attempted to add enough crystalline content to their proposed drugs to persuade the federal courts that their drugs do not infringe the GSK patents covering CEFTIN®, while at the same time arguing to FDA that their new drugs are identical to CEFTIN®. The crystalline content in the proposed drugs is not an impurity or an inert ingredient, and was not added to improve the drugs' safety or efficacy. Instead, it makes the drugs less stable, harder to manufacture in consistent lots, and less absorbable than the amorphous form. FDA endorsement of this regulatory charade, in which generic manufacturers tamper with the crystalline structure and stereoisomeric mixture of reference listed drugs to avoid innovator patents, could create a new loophole undermining the patent laws, flooding FDA with generic applications for inferior products, potentially jeopardizing the health of vulnerable children and diminishing physician/consumer confidence in the equivalency of generic products.

Additionally, as discussed herein, GSK, the manufacturer of the pioneer drug CEFTIN®, has commenced patent infringement actions against two of the generic manufacturers that have filed ANDAs for new drugs containing cefuroxime axetil. Any FDA approval of these ANDAs should,

therefore, be stayed until either: (1) a court issues a final judgment regarding the validity and infringement of GSK's patent; or (2) 30 months have elapsed from the date GSK filed suit.

Finally, it is respectfully submitted that FDA should initiate rulemaking proceedings to set uniform standards for ANDAs in which applicants seek to bypass existing innovator product patents by proposing new drugs that contain different crystalline forms and/or different stereoisomeric mixtures of the active ingredient in a reference listed drug. Generic manufacturers are embracing this strategy as a means to achieve expedited review and approval of their proposed new drugs while avoiding the innovator patents, despite the fact that the safety and efficacy of the active ingredients in their proposed new drugs have never been adequately tested. Uniform standards should be developed to deal with this issue, so that innovators, generic manufacturers and the public all have notice of the standards to which such proposed deviations from reference listed drugs will be held.

This Petition raises significant issues of statutory construction and public policy. Accordingly, to the extent that FDA is not inclined to grant some or all of the relief requested herein, PDI respectfully requests that FDA issue a written record of decision that sets forth in detail the legal and factual grounds for FDA's decision, in order to facilitate judicial review thereof.

## **2. Factual Background**

### **a. CEFTIN® (amorphous cefuroxime axetil)**

PDI is the exclusive distributor in the United States of CEFTIN®, a broad-spectrum cephalosporin antibiotic manufactured by GSK and sold by prescription in tablet and powder forms.<sup>1</sup> CEFTIN®

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<sup>1</sup> GSK and PDI entered into a five year Agreement for the distribution, sale and marketing of CEFTIN® in September 2000.

Tablets are indicated for the treatment of a range of conditions, including pharyngitis/tonsillitis, acute bacterial otitis media, acute bacterial maxillary sinusitis, acute bacterial exacerbations of chronic bronchitis and secondary bacterial infections of acute bronchitis, uncomplicated skin and skin-structure infections, uncomplicated urinary tract infections, uncomplicated gonorrhea and early Lyme disease (erythema migrans). CEFTIN® for Oral Suspension, used primarily by small children, is indicated for the treatment of acute bacterial otitis media, impetigo and pharyngitis/tonsillitis.

The active ingredient in CEFTIN® as listed in its FDA-approved product labeling is amorphous cefuroxime axetil. GSK's new drug application NDA for CEFTIN® Tablets (amorphous cefuroxime axetil) was approved by FDA in 1987, and its application for CEFTIN® for Oral Suspension (amorphous cefuroxime axetil) was approved by FDA in 1994.

**b. Cefuroxime Axetil**

Cefuroxime axetil can take a number of solid state forms, some amorphous and some crystalline. These forms include: (i) amorphous isomer A; (ii) amorphous isomer B; (iii) three forms of crystalline isomer A known as AI, AII and AIII (a dioxane solvate); and (iv) two forms of crystalline isomer B -- BI (anhydrous) and BII (hemihydrate). There is a clear consensus in the scientific community that each of these different forms has a different solubility and different bioavailability.<sup>2</sup> CEFTIN®, the only cefuroxime axetil drug that FDA has reviewed and approved to date, is comprised of a strictly amorphous combination of isomers A and B in a fixed ratio.

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<sup>2</sup> PDI understands that GSK has previously submitted a Citizen's Petition that discusses, and attaches, certain studies that address the varying absorption rates and bioavailability of the different solid state forms of cefuroxime axetil. To the extent that GSK's Citizen's Petition seeks the same relief as that requested in this Petition and cites evidence in support thereof, PDI relies upon, and incorporates herein by reference, GSK's Citizen's Petition (together with its accompanying exhibits and supplemental Citizen's Petitions) and the evidence cited therein. Additional scientific studies and literature are discussed *infra*.

**c. The Proposed Generic Drugs**

PDI understands that several generic manufacturers have filed ANDAs seeking approval of drug products containing as their active ingredient a mixture of crystalline and amorphous cefuroxime axetil. Applications based on these combinations have been made not to create a more easily absorbed or superior antibiotic, but rather to avoid a patent held by the innovator company on the amorphous form of the active ingredient. Ranbaxy, for example, has submitted an ANDA seeking approval to market a drug product containing cefuroxime axetil that is 10% to 15% crystalline. To date, FDA has not approved any form of cefuroxime axetil that is crystalline or that comprises both crystalline and amorphous cefuroxime axetil. Likewise, no adequate and well-controlled clinical studies have been conducted to ascertain the safety or efficacy of such drug products. On the contrary, the only form of cefuroxime axetil that FDA has reviewed and approved, and the only form for which safety and efficacy has been demonstrated through substantial clinical evidence, is the amorphous cefuroxime axetil contained in CEFTIN®.

**d. The Pending Patent Litigation**

Because CEFTIN® is an antibiotic approved under the now-repealed § 507 of the FFDCAs, its corresponding patents are not listed in FDA's *Approved Drug Products With Therapeutic Equivalence Evaluations* (the "Orange Book"). Accordingly, ANDA applicants seeking approval for a generic version of cefuroxime axetil have not been required to include in their ANDAs a paragraph (I), (II), (III) or (IV) certification for the GSK patents that cover CEFTIN®, and have not been required to give notice of their ANDA filings to GSK. While FDA generally does not base ANDA approvals on review of patent status, some discussion of patentability is important to the Agency's understanding of the Ranbaxy product (among others) and the legal issues presented in this Petition. As the GSK patents covering CEFTIN® are not listed in the Orange Book, FDA likely has not received any of the information provided below in the ANDAs filed by Ranbaxy and Apotex.

In or around the fall of 2000, GSK discovered that at least two generic manufacturers, Ranbaxy and Apotex, had filed ANDAs for generic cefuroxime axetil, and determined that their proposed drugs would infringe its U.S. Patent No. 4,562,181 (which claims amorphous cefuroxime axetil). (A copy of the '181 patent is appended hereto as Attachment 1.) Accordingly, GSK filed actions for patent infringement against them. GSK filed its complaint against Apotex in the United States District Court for the Northern District of Illinois on or about September 22, 2000, and filed its complaint against Ranbaxy in the United States District Court for the District of New Jersey on or about October 20, 2000. (Copies of the Apotex and Ranbaxy complaints are appended hereto as Attachments 2 and 3, respectively.)

Neither federal court has yet issued a final order or judgment regarding the validity or infringement of GSK's '181 patent. In *Apotex*, GSK recently was granted leave to amend its complaint to add claims under a second patent. That case is still in the discovery phase. In the *Ranbaxy* litigation, the District Court entered a preliminary injunction against Ranbaxy on December 21, 2000, finding that GSK was likely to succeed on the merits of its infringement claims. On August 20, 2001, the Federal Circuit vacated that injunction and remanded the case back to the District Court for a full trial on the merits. The Court of Appeals' decision was based, in part, on its application of its recent decision in *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*, 234 F. 3d 558 (Fed. Cir. 2000) (en banc), despite the fact that the United States Supreme Court has granted *certiorari* to review in this fall term the rule of law laid down in that case. To date, there has been no final adjudication of either *Festo* or the *Ranbaxy* case.

**3. ANDAs Cannot Be Accepted, and Cannot Be Approved, for New Drugs Containing a Mixture of Amorphous and Crystalline Cefuroxime Axetil.**

As a general matter, an applicant seeking FDA approval for a new drug must file an NDA that conforms to the requirements set forth in 21 U.S.C. § 355(b)(1). The content and format of an NDA are set forth in 21 C.F.R. § 314.50. The NDA process requires an applicant to submit a wide range of detailed

information and extensive scientific evidence, including adequate and well-controlled clinical studies, from which FDA can make informed decisions regarding the safety and effectiveness of the proposed new drug for its intended use.

In certain circumstances, applicants may file applications that include less than all the information required for a full NDA, by filing either an application pursuant to 21 U.S.C. § 355(b)(2) (a "505(b)(2) application") or by filing an ANDA pursuant to 21 U.S.C. § 355(j). The circumstances in which such alternate applications may be filed are narrowly and strictly defined. None of these circumstances allows an applicant to submit, or FDA to approve, an ANDA or 505(b)(2) application for a drug that contains active ingredients that are different than, or in addition to, those contained in the innovator drug. More specifically, none of these circumstances permits the submission or approval of an ANDA or 505(b)(2) application for a proposed new drug containing both crystalline and amorphous cefuroxime axetil as its active ingredients.<sup>3</sup>

**a. ANDAs Should Not Be Accepted for New Drugs Containing a Mixture of Amorphous and Crystalline Cefuroxime Axetil.**

There are only two types of drugs for which an ANDA may be submitted:

- (1) An ANDA may be submitted for a drug product that is "the same as" a listed drug. 21 C.F.R. § 314.92. FDA regulations make clear that "[f]or determining the suitability of an abbreviated new drug application, the term 'same as' means *identical in active ingredient(s)*, dosage form, strength, route of administration, and conditions of use, except that conditions of use for which approval cannot be

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<sup>3</sup> So far as PDI is aware, no generic manufacturer has attempted to submit a 505(b)(2) application for a new drug containing a mixture of crystalline and amorphous cefuroxime axetil. Accordingly, this Petition will be addressed solely to the nonsuitability of the ANDA process for such drugs.

granted because of exclusivity or an existing patent may be omitted." *Id.*  
(emphasis added).

- (2) An ANDA may be submitted for a drug product that FDA declares suitable for an ANDA submission through its approval of an applicant's petition to request a change from a listed drug. *See* 21 C.F.R. § 314.92. These petition procedures, which are specified in 21 U.S.C. § 355(j)(2)(C) and detailed in 21 C.F.R. § 314.93, expressly forbid approval of *any* petition that seeks to change the active ingredient of a listed drug that is not a combination drug (*i.e.*, a drug that does not contain more than one active ingredient). *See* 21 C.F.R. § 314.93(e)(1) (stating that FDA will approve properly submitted petitions to request a change from a listed drug *unless* one of five enumerated circumstances is present).

Applications for new drugs containing both crystalline and amorphous cefuroxime axetil do not fall within either of these two categories in which FDA has express statutory authority to approve an ANDA. Accordingly, ANDAs may not be submitted, and cannot be approved, for these new drug products.

- (1) **A Mixture of Amorphous and Crystalline Cefuroxime Axetil Is Not "the Same as" Amorphous Cefuroxime Axetil, Which Is the Active Ingredient in CEFTIN®.**
- (A) **The Scientific Community Is in Strong Agreement that Crystalline Cefuroxime Axetil, and Mixtures of Amorphous and Crystalline Cefuroxime Axetil, Are Not "the Same as" Amorphous Cefuroxime Axetil.**

The FDA-approved active ingredient in CEFTIN® is amorphous cefuroxime axetil with a fixed ratio of R- and S- stereoisomers. The drug professional labeling approved by FDA as a condition to approval of GSK's NDA states in the second paragraph that "Cefuroxime axetil is in the amorphous form."

*Physician's Desk Reference*, at 1358 (55<sup>th</sup> ed.) (2001). (Attachment 4.) A mixture of amorphous and crystalline cefuroxime axetil is undeniably *not* "the same as" – *i.e.*, identical to – amorphous cefuroxime axetil. *See, e.g.*, Irena Oszczapowicz, Bozena Tejchman, Andrzej Zimniak and Janusz Oszczapowicz, *Esters of Cephalosporins. Part VI. Properties of the  $\beta$ -Form of 1-Acetoxyethyl Ester of Cefuroxime*, *Acta Polon. Pharm. - Drug Research* Vol. 55 No. 3, at 197-204 (1998) (hereinafter "Oszczapowicz *et al.*") (Attachment 5); Caroline M. Perry, Rex N. Brogden, *Cefuroxime Axetil: A Review of Its Antibacterial Activity, Pharmacokinetic Properties and Therapeutic Efficacy*, *Drugs* 1996 Jul; 52(1):125-158 (hereinafter "Perry & Brogden") (Attachment 6). GSK has cited several additional studies in its Citizen's Petition showing, among other things, the differences in absorption rate and rate of recrystallization between crystalline and amorphous cefuroxime axetil. PDI incorporates those portions of GSK's Petition and its accompanying exhibits (including the supplements thereto) herein by reference.

The distinction between amorphous and crystalline cefuroxime axetil is not hypothetical or a matter of academic speculation. On the contrary, the references cited in both this Petition and GSK's Petition demonstrate a solid, science-based consensus that:

1. Crystalline cefuroxime axetil's physiological properties are significantly different than those of amorphous cefuroxime axetil.
2. There are several crystalline forms of cefuroxime axetil, each of which has significantly different physiological properties.

These differences in physiological properties relate to solubility in gastric juice (as contrasted with other organic solvents), particle size, rates of de-esterification and, ultimately, bioavailability. These are precisely the sort of differences that are of concern in considering whether a proposed new drug can be considered "the same as" and/or bioequivalent to a known and tested drug.

In the preamble to its regulations governing ANDA submissions, for example, FDA has advised that:

FDA will consider an active ingredient to be the same as that of the reference listed drug if it meets the same standards for identity. In most cases, these standards are described in the U.S. Pharmacopeia (U.S.P.) However, in some cases, FDA may prescribe *additional standards* that are *material to the ingredient's sameness*. For example, *for some products, standards for crystalline structure or stereoisomeric mixture may be required.*

57 Fed. Reg. 17950, 17959 (Apr. 28, 1992) (emphasis added). *See also, e.g.,* Draft ICH Guidance "Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances," 62 Fed. Reg. 62,890 (Nov. 25, 1997) (proposing guidelines for determining when acceptance criteria for polymorphism are warranted for a new drug substance) (Attachment D to GSK's Petition).

European regulatory agencies, too, have recognized that variation in the physiological properties of different crystalline forms of a drug substance must be carefully evaluated and that, if those properties are found to be important to the quality of the product, they should be controlled pursuant to predetermined acceptance criteria. *E.g.,* The European Agency for the Evaluation of Medicinal Products, Human Medicines Evaluation Unit, Committee for Proprietary Medicinal Products, *Note for Guidance on Development of Pharmaceuticals*, at 1-5 (Jan. 28, 1998) (Attachment 7).

In this case, there is strong scientific evidence to show that both the crystalline structure and the stereoisomeric mixture of cefuroxime axetil can have a material impact on the drug's solubility and bioavailability. Both of these factors can be controlled through appropriate manufacturing processes. Accordingly, acceptance criteria should be developed to control both the crystallinity and stereoisomeric mixture of cefuroxime axetil drug products. To the extent a new drug is proposed that demonstrates the

same crystallinity and stereoisomeric mixture as the cefuroxime axetil in CEFTIN®, an ANDA may be a suitable vehicle for pursuing that application (assuming all other ANDA criteria are satisfied). If, however, a new drug is proposed that is materially different from CEFTIN® in terms of its crystallinity or stereoisomeric mixture, then that drug should be carefully evaluated through the more comprehensive NDA process.

**(B) ANDA Applicants Admit that a Mixture of Crystalline and Amorphous Cefuroxime Axetil Is Not the Same as Amorphous Cefuroxime Axetil.**

The ANDA applicants who seek approval for generic cefuroxime axetil admit that the mixture of crystalline and amorphous cefuroxime axetil in their proposed drugs is not "the same as" the amorphous cefuroxime axetil in CEFTIN® -- a concession that should be a death knell for their ANDA filings.

Ranbaxy, for example, has freely admitted in its ANDA that the active ingredient of its proposed drug "is a mixture of cefuroxime axetil (amorphous) and cefuroxime axetil (crystalline), *whereas, the active ingredient of Cefitin® Tablets is amorphous cefuroxime axetil.*" April 19, 1999 Letter from Ranbaxy to Office of Generic Drugs, at 2 (emphasis added) (Attachment 8). Ranbaxy representatives also have testified that:

[t]he crystalline cefuroxime axetil in Ranbaxy's cefuroxime axetil antibiotic is not an unavoidable impurity or a trace component, but is a *necessary and active part of the drug product.*

Declaration of Shirley Ternyik in Support of Ranbaxy Pharmaceuticals Inc.'s Opposition to Plaintiffs' Motion for a Preliminary Injunction, at ¶ 6 (emphasis added) (Attachment 9).

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In defending against GSK's patent infringement claims, Ranbaxy repeatedly has emphasized to the federal courts that the addition of crystalline cefuroxime axetil to its proposed drug represents a significant departure from the previously-approved CEFTIN®, asserting that:

Ranbaxy did *not* add an inert component to amorphous cefuroxime axetil in an attempt to avoid infringement. What Ranbaxy did do is *develop an antibiotic that uses both crystalline and amorphous cefuroxime axetil as active components* to deliver the active moiety to the patient. Thus, Ranbaxy developed a *new and useful antibiotic*, while at the same time avoiding Glaxo's patent.

Reply Brief of Defendant-Appellant Ranbaxy Pharmaceuticals, Inc., at 28 (emphasis added) (Attachment 10).

Ranbaxy has further asserted that:

[t]he unrebutted evidence shows that the *crystalline* cefuroxime axetil in Ranbaxy's antibiotic "is an *active ingredient*" . . . and thus an essential part of the drug product.

Nonconfidential Brief of Defendant-Appellant Ranbaxy Pharmaceuticals Inc., at 24 n.4 (emphasis added) (Attachment 11).

By Ranbaxy's own admission, therefore, its proposed new drug is a combination drug containing *two* active ingredients – crystalline cefuroxime axetil and amorphous cefuroxime axetil – and is a “new and [purportedly] useful antibiotic,” not to be confused with the reference listed drug CEFTIN®. Ranbaxy's proposed combination drug, then, is precisely the sort of new drug product which should be reviewed through the NDA process, so that FDA can consider carefully evidence from the adequate and well-

controlled clinical trials that must be conducted to ensure its safe and efficacious use at such optimal doses as are determined through the research.

**(C) ANDA Applicants Are Trying (Unsuccessfully) to Walk a Fine Line Between Patent Infringement and Regulatory Disapproval of Their New Drug Applications.**

Ranbaxy has embraced the differences between its proposed new combination drug and CEFTIN®-brand amorphous cefuroxime axetil under oath in court to prove that its mixture of crystalline and amorphous cefuroxime axetil is not the same drug as GSK's patented amorphous cefuroxime axetil. At the same time, however, Ranbaxy asks this Agency to ignore the significant differences between its combination drug and CEFTIN® touted in court, and to find instead that the two products in fact contain the same drug.

This is, of course, an awkward position for Ranbaxy (and for any other new drug applicant seeking, on the one hand, to obtain FDA approval for cefuroxime axetil as the same identical drug through the filing of an ANDA, while at the same time seeking to avoid liability for infringement of GSK's patent through the manufacture of a different drug). If a combination drug containing a mixture of crystalline and amorphous cefuroxime axetil is "the same as" -- *i.e.*, "identical to" -- pure amorphous cefuroxime axetil, then these ANDA applicants must run afoul of GSK's patent. If, on the other hand, the two forms of cefuroxime axetil are different, then the new drug applicants are statutorily ineligible to use the ANDA procedure. These are the scientifically consistent positions with which ANDA applicants seeking approval for a generic cefuroxime axetil product are confronted, and neither allows them to market their products. Ranbaxy, therefore (joined, perhaps, by other ANDA applicants), has pursued the only option remaining to it: it has adopted scientifically inconsistent positions in the hope that FDA will not take notice of the judicial record.

Thus, while conceding (and, indeed, emphasizing) the significant differences between its proposed new combination drug and the approved single ingredient amorphous cefuroxime axetil, Ranbaxy has argued that by manipulating the delivery vehicle of its combination of amorphous and crystalline cefuroxime axetil, it can achieve roughly the same ultimate clinical effect as is obtained with amorphous cefuroxime axetil. This position is fatally flawed on both legal and scientific grounds.

First, as a legal matter, now that Ranbaxy has conceded that crystalline cefuroxime axetil has different physiological properties than those of amorphous cefuroxime axetil (as it must), and that the two drugs are not "identical," it has established conclusively its ineligibility for ANDA approval for its combination drug product in which both crystalline and amorphous cefuroxime axetil are active ingredients. The ANDA procedure was established to allow a manufacturer of the same drug to avoid re-demonstrating the safety and efficacy of the *same* drug for which these properties had already been demonstrated. The ANDA allows a generic manufacturer to sell the *same* drug, in the *same* dose and the *same* dosage form, labeled for the *same* indications (with some exceptions not applicable here). This summary application can be made once the manufacturer demonstrates its ability to manufacture its new drug in a way that results in the *same* availability and effect as the original drug. That is not what Ranbaxy and other proponents of the pending ANDAs propose to do. Rather, they seek permission to take an unlisted drug that is conceded to have inferior solubility and availability, and to modify its dosage form to achieve a clinical effect purportedly comparable to the listed drug. Even if one assumes that there is good science to support their claims to be able to achieve this result, the ANDA procedure is simply the wrong statutory vehicle for obtaining regulatory approval. An NDA is required.

Second, as a scientific matter, the proponents of the pending ANDAs are selling damaged goods. At the heart of their position is the assumption that the inferior properties of crystalline cefuroxime axetil can be adjusted by means of dosage form compounding to result in a product more or less equivalent to amorphous cefuroxime axetil. The simple truth of the matter is that there is no basis in good science for such a position. The scientific community has been down this path before. Amorphous cefuroxime axetil was approved for use in the United States only after long experience with various crystalline

forms. Clinical testing demonstrated that crystalline compounds could not be used reliably because they could not be formulated in stable forms with consistent potency. *See, e.g., Perry & Brogden, supra*, at 134 (and references cited therein). The literature is full of reports concerning the variations in the solubility and bioavailability between different crystalline forms of cefuroxime axetil as well as conflicting reports concerning these parameters for any given crystalline form.

In a patent application, for example, ACS Dobfar, S.p.A. reported the discovery of a  $\beta$  crystalline form of cefuroxime axetil with enhanced bioavailability that was comparable to that of amorphous cefuroxime axetil. *See* European Patent Application No. 0757991 A1 (1995) (Attachment 12). Dobfar's results, however, could not be replicated. In fact, those results subsequently were contradicted in the scientific literature. *Oszczapowicz et al., supra*. In its Citizen's Petition, GSK cites as another example Eli Lilly's apparent inability to substantiate claims that it purportedly could achieve bioequivalence to CEFTIN® with a drug containing crystalline cefuroxime axetil or a mixture of crystalline and amorphous cefuroxime axetil. *See* GSK Citizen's Petition, at 4 n.3 (citing FDA Docket No. 87-N-0317). In short, there is no basis in sound science, and no consensus among researchers in the field of cefuroxime axetil, that the inferior stability, activity, solubility, and availability of crystalline cefuroxime axetil, or a mixture of amorphous and crystalline cefuroxime axetil, can reliably be modified by any known technique to approximate that of amorphous cefuroxime axetil.

It is respectfully submitted that the acceptance of a mere *ipse dixit* from Ranbaxy or other ANDA applicants in the face of a contradictory body of scientific evidence would be clear error. Approval of the pending ANDAs on the basis of the applicants' untested assertions that they have been able to accomplish and reproduce what sophisticated entities have not would abandon science-based decision making in the interest of economic expediency and ignore the clear statutory mandate requiring "sameness." Such an arbitrary result is illegal. It is also unwise because it will encourage many similar applications for inferior or less stable drugs. Applications will be based on efforts to engineer around patents rather than on improving science. FDA will be left to use scarce resources to review many more generic applications and monitor many more difficult manufacturing practices. Subpotent doses could

cause bacterial resistance in the most vulnerable patient population. Consumers could come to doubt the equivalence of generics or the efficacy of FDA's generic approval standards. The statutory scheme of the FFDCA, which permits ANDA filings only for drugs that truly are the *same* as a reference listed drug, is intended -- and must be used -- to forestall these problems.

**(D) The "Close Enough" Standard Urged by ANDA Applicants Cannot Be Reconciled with the Plain Language of the FFDCA.**

The efforts by Ranbaxy and other ANDA applicants to persuade FDA that their proposed mixtures of active ingredients are "close enough" to CEFTIN®'s amorphous cefuroxime axetil simply cannot stand in light of the clear statutory mandate summarized above. FDA has clarified in its regulations that "same as" means "identical to" the reference listed drug. FDA also has persuasively argued this narrow position to federal appellate courts and reemphasized it in published regulations and guidances.

As FDA recently explained to the United States Court of Appeals for the District of Columbia Circuit, FDA has construed the statutory requirement of "sameness" to mean that a generic manufacturer must be held to the same standards of chemical identity as those established by the pioneer drug. *Serono Labs., Inc. v. Shalala*, 158 F.3d 1313, 1320 (D.C. Cir. 1998). FDA advised the Court of Appeals that:

[t]he agency . . . endeavor[s] to guarantee the greatest degree of "sameness" possible for this kind of product, *by ensuring an identical chemical structure where possible* (in the primary structure), while reducing natural batch-to-batch variance . . . *to the same degree as that found in the pioneer drug.*

*Id.* (emphasis added).

FDA specifically requires the crystalline structure and stereoisomeric mixture of new drugs to be identical to those of a pioneer drug for substances in which these physiological properties are material to the drug's chemical identity. *See* 57 Fed. Reg. 17950, 17959 (Apr. 28, 1992).

In a separate policy statement, FDA advised that:

Diastereoisomers and geometric isomers are both chemically distinct and pharmacologically different (unless they are interconverted *in vivo*) and are generally readily separated without chiral techniques. Geometric isomers and *diastereoisomers* therefore should, with the rare exception of cases where *in vivo* interconversion occurs, be treated as *separate drugs* and developed accordingly.

FDA's Policy Statement for the Development of New Stereoisomeric Drugs (May 1, 1992) (emphasis added) (Attachment 13).

In the case of cefuroxime axetil, it is both possible and necessary to control the crystalline structure and stereoisomeric mixture of the drug. Scientific study has proven that these traits have a significant impact on the solubility, bioavailability and stability of the drug substance. *See, e.g.,* Oszczapowicz *et al., supra*; Declaration of Dr. Stephen Byrn (Exhibit E to GSK's Citizen's Petition); *see also* GSK Citizen's Petition (citing and discussing other scientific evidence showing substantial impact of crystalline structure on solubility and bioavailability of cefuroxime axetil). Indeed, one of Ranbaxy's own patents is directed specifically to a manufacturing process that converts S-isomer cefuroxime axetil into R-isomer cefuroxime axetil which, according to Ranbaxy, demonstrates superior bioavailability and absorption. *See* U.S. Patent No. 6,235,896 (Attachment 14).

CEFTIN®, the reference listed drug, contains (and must continue to contain under the terms of GSK's NDA) amorphous cefuroxime axetil with a fixed ratio of R- and S- isomers. There is no question that it

is possible to manufacture amorphous cefuroxime axetil with this structure and this stereoisomeric mixture consistently and uniformly. Indeed, both GSK and Ranbaxy hold patents that describe processes which ensure such consistent manufacture. *See* U.S. Patent No. 4,562,181 (GSK patent for amorphous cefuroxime axetil) (Attachment 1); U.S. Patent No. 6,235,896 (Ranbaxy patent entitled "Process for the Preparation of Cefuroxime") (Attachment 14); *see also* U.S. Patent No. 6,060,599 (Ranbaxy patent entitled "Process for the Preparation of Cefuroxime Axetil in an Amorphous Form") (Attachment 15). There also is no question that changes to the crystalline structure and stereoisomeric mixture of cefuroxime axetil will alter, at a minimum, the solubility and bioavailability of the drug. There is, therefore, no justification to allow generic manufacturers to deviate from the standards of chemical identity of cefuroxime axetil to which CEFTIN® has been, and will continue to be, held.

This case, therefore, differs from *Serono*, in which not even the pioneer drug manufacturer could demonstrate consistent chemical identity of its drug substance. On the contrary, the generic manufacturers who presently seek approval for new drugs containing a mixture of crystalline and amorphous cefuroxime axetil are capable of manufacturing amorphous cefuroxime axetil with a fixed stereoisomeric structure, just as GSK is. The ANDA applicants simply do not want to use this preferred and proved method of manufacture, because to manufacture such a drug they either must wait for the expiration of GSK's '181 patent in July 2003 or license the patent from GSK and pay the attendant royalties to the patent holder.

Instead, these generic manufacturers have tried to develop a form of cefuroxime axetil that is *not* "the same as" the amorphous cefuroxime axetil in CEFTIN®, hoping that these alternate compositions will be "close enough" – close enough to get FDA approval with only a showing of bioequivalency and bioavailability while different enough to escape liability for infringing existing innovator patents. Indeed, Ranbaxy has been quite candid in admitting that it added crystalline cefuroxime axetil to its drug product solely in order to get around GSK's patent. *See, e.g.*, Excerpts from November 9, 2000 Transcript of Deposition of Dipak Chattarj, President of Ranbaxy Pharmaceuticals, Inc., at 27-36 (in which Mr. Chattarj was asked, among other things, "[d]id the awareness of the [GSK] patent affect your

picking the crystallinity level” for Ranbaxy’s proposed new drug product, to which Mr. Chattarj responded, “[e]ntirely”) (emphasis added) (Attachment 16).

The American law does not permit such maneuvering as Ranbaxy and other foreign and domestic generic manufacturers have tried. There is no “close enough” standard in the FDCA or in FDA’s corresponding regulations. Rather, the law is clear and unambiguous – the active ingredient in a new drug must be “the same as” that of the pioneer, or else the NDA and not the ANDA process must be used. It would constitute unfair regulatory manipulation and abuse of the discretion of the Agency to interpret “same” or “identical” active ingredient to mean that 10-15% crystalline cefuroxime axetil = amorphous cefuroxime axetil.

**(E) Recent Amendments to the USP Monograph Do Not Make the Proposed Combination Drugs Approvable.**

Generic manufacturers have persuaded the United States Pharmacopeia (“USP”) to amend its monograph effective September 30, 2001, to recognize two formulations of cefuroxime axetil. This decision by USP does not change the fact that proposed generic drug products containing a mixture of amorphous and crystalline cefuroxime axetil do not contain the “same” active ingredient as CEFTIN®. The USP manufacturing standard and the FDA standard for ANDA approval are not the same. While the USP may be a starting point for FDA’s evaluation of “sameness” (or bioequivalency), it does not end FDA’s inquiry. Indeed, FDA expressly has recognized that USP monographs merely establish a minimum threshold for drug identity. *E.g.*, 57 Fed. Reg. 17950, 17959 (Apr. 28, 1992). FDA may impose additional requirements as needed on proposed new drugs to ensure their chemical identity with listed drugs in all material respects. *Id.*

Importantly, even as amended, the USP monograph is careful to distinguish between crystalline and amorphous cefuroxime axetil, to the point of requiring drugs to specify in labeling which form of the compound comprises their active ingredient. USP 24 Supplement, at 3202 (Aug. 1, 2001) (effective as

of September 30, 2001) (Attachment 17). The amended Description and Solubility/Reference Tables also distinguish between the two forms of the ingredients: the "amorphous form" is listed as "soluble in chloroform, in ethyl acetate and in methanol," while the "crystalline form" is listed as "sparingly soluble in chloroform, in ethyl acetate and in methanol." *Id.*

Even with its new amendments, therefore, the USP monograph for cefuroxime axetil will not permit drugs containing crystalline cefuroxime axetil, or a mixture of crystalline and amorphous cefuroxime axetil, to be labeled in the same manner as amorphous cefuroxime axetil. As discussed below, and as noted in GSK's Citizen's Petition and its supplements thereto, this fact alone forbids approval of any ANDA for a new drug containing a mixture of crystalline and amorphous cefuroxime axetil. *See* 21 U.S.C. § 355(j)(4)(G) (barring approval of an ANDA if FDA finds that labeling for the proposed drug is not "the same as" that of the listed drug, with certain limited exceptions). Here, too, it would constitute an abuse of the Agency's discretion to interpret the listing of a "15% crystalline cefuroxime axetil" to be the same labeling as "Cefuroxime axetil is in the amorphous form."

**(2) The Generic Manufacturers Cannot Petition to Request a Change in Active Ingredients Pursuant to 21 U.S.C. § 355(j)(2)(C) to Save Their ANDA Submissions.**

As set forth above, the pending ANDAs for new drugs containing a mixture of crystalline and amorphous cefuroxime axetil cannot satisfy the statutory criteria for ANDA approval because, among other things, the proposed mixtures of crystalline and amorphous cefuroxime axetil plainly cannot be considered the same as amorphous cefuroxime axetil, as required by law. The only avenue for these new drug applicants to avoid rejection of their ANDAs, therefore, is to seek leave to depart from the statutory criteria for ANDA approval by filing a petition to request a change from the listed drug, CEFTIN®. 21 C.F.R. § 314.93.

To our knowledge, none of the generic manufacturers has filed such a petition. Moreover, it is likely that FDA would have to deny any such petition in any event.

FDA can accept a petition to change an active ingredient only in express regulatory circumstances listed in 21 C.F.R. § 314.93(b). These circumstances include: (a) a change in route of administration, dosage form or strength from a listed drug; or (b) a substitution of one active ingredient in a listed combination drug. Petitions to submit ANDAs for any other changes from a listed drug *will not* be approved. 21 C.F.R. § 314.93(a). A petition *must* be disapproved if it "seeks to change an active ingredient" in a drug product that is not a combination drug. 21 C.F.R. § 314.93(e)(ii). CEFTIN® is not a combination drug, as it contains only one listed active ingredient: "cefuroxime axetil in the amorphous form."

Ranbaxy, Apotex, and other ANDA applicants seeking approval for drugs containing a mixture of crystalline and amorphous cefuroxime axetil have proposed a change from CEFTIN®, the listed drug. Indeed, Ranbaxy states quite candidly in its ANDA that the active ingredient in its proposed drug is *not* the same as that in CEFTIN®. Ranbaxy and the other ANDA applicants, however, have sought to bypass the petition change procedure -- a procedure that clearly states that their proposed change, a variation in the active ingredient of a non-combination product, *cannot be approved* for an ANDA.

This petition process was designed to consider active ingredient changes such as that which Ranbaxy and others have proposed. The process requires the filing of a petition requesting a change from the listed drug, amorphous cefuroxime axetil. The process also requires that the proposed change must be rejected.

**b. ANDAs for a New Drug Containing a Mixture of Crystalline and Amorphous Cefuroxime Axetil Fail to Meet the Statutory Requirements of "Sameness" in Active Ingredient and Drug Product Labeling.**

FDA has no discretion to approve ANDAs that either: (1) do not comply with the eight criteria mandated by 21 U.S.C. § 355(j)(2)(A); or (2) are not the subject of a previously approved petition requesting a change to a listed drug. If an ANDA applicant fails to prove, among other things, that (1)

the active ingredient in its proposed drug is the same as that of a listed drug, and (2) the labeling for its proposed drug will be the same as that of a listed drug (with some limited exceptions), and is not otherwise granted leave to change the listed drug, FDA *cannot* approve the application. *See* 21 U.S.C. § 355(j)(4)(i)-(viii).<sup>4</sup>

In this case, the ANDA applicants seeking approval for drugs containing a mixture of amorphous and crystalline cefuroxime axetil cannot meet the requirement that their drugs contain an active ingredient that is "the same as" that in CEFTIN®. *See supra*, at B.3.a.(1).

Moreover, these ANDA applicants cannot satisfy the requirement that their labeling must be "the same as" that of CEFTIN®, the listed drug. 21 U.S.C. § 355(j)(2)(A)(v). As the newly amended USP monograph for cefuroxime axetil makes clear, drugs containing cefuroxime axetil must specify whether they contain cefuroxime axetil in amorphous form, crystalline form, or a mixture of both. If the drug contains a mixture of amorphous and crystalline cefuroxime axetil, the drug product label must specify the ratio of each ingredient. USP 24 Supplement, at 3202 (Aug. 1, 2001) (effective as of Sept. 30, 2001). Labeling for the new drugs proposed by these ANDA applicants, therefore, *cannot* be "the same as" that of CEFTIN®, as required by the FFDCA, and still conform to the revised USP monograph.<sup>5</sup>

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<sup>4</sup> In its patent infringement litigation, and before FDA itself, Ranbaxy has suggested that if its proposed new drug is bioequivalent to amorphous cefuroxime axetil, then that drug should also be considered "the same as" amorphous cefuroxime axetil. *See, e.g.*, Reply Brief of Defendant-Appellant Ranbaxy Pharmaceuticals, Inc., at 31-32 (contending that FDA can approve its proposed drug despite "differences in physical form" because Ranbaxy purportedly has demonstrated bioequivalence). Ranbaxy apparently hopes to conflate two separate and independent criteria in the FFDCA, 21 U.S.C. § 355(j)(2)(ii) (sameness) and (j)(2)(iv) (bioequivalence), each of which must be satisfied before an ANDA can be approved. Ranbaxy's argument would render section 355(j)(2)(ii) of the FFDCA superfluous – a construction that is flatly prohibited under the law. *E.g., Duncan v. Walker*, 531 U.S. 991, 121 S. Ct. 2120, 2125 (2001).

<sup>5</sup> FDA regulations permit differences in labeling *only* with regard to "expiration date, formulation, bioavailability, or pharmacokinetics, labeling revisions made to comply with current FDA guidelines or other guidance, or omission of an indication or other aspect of labeling protected by

Therefore, because Ranbaxy and the other ANDA applicants cannot satisfy the eight criteria for ANDA approval mandated by 21 U.S.C. § 355(j)(2), and because these applicants have not filed and cannot file a petition for leave to deviate from these criteria, any approval of their ANDAs would constitute an arbitrary and capricious departure from the plain language of the FDCA.

**3. Any Approval of the Ranbaxy or Apotex ANDAs for Generic Cefuroxime Axetil Should Be Stayed Pursuant to 21 U.S.C. § 355(j)(5)(B).**

Section 505(j)(5)(B) of the FDCA, which controls the effective date for FDA approval of an ANDA, imposes a 30-month stay on that approval if a patent holder files an infringement action against the ANDA applicant within 45 days of receiving notice of that applicant's filing of a paragraph (IV) certification with regard to one of the patent holder's patents. 21 U.S.C. § 505(j)(5)(B). This statutory provision is intended to preserve the balance between the interest in allowing generic drugs to come quickly to market and the need to protect the integrity of issued patents and ensure that those patents are enforced for their full statutory terms. It also is intended to allow all parties to determine their respective rights under an issued patent *before* any generic product goes to market. *See, e.g., Ben Venue Labs., Inc. v. Novartis Pharm. Corp.*, 146 F. Supp. 2d 572, 578 (D.N.J. 2001) (noting that the purpose of the 30-month stay "is to allow the patent infringement action to be litigated in court, and to give assurances to innovator companies that generic manufacturers will not immediately proceed to market after receiving approval of their ANDAs").

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Continued from previous page

patent or accorded exclusivity." 21 C.F.R. § 314.94(a)(8)(iv). The USP-required labeling to identify the form of cefuroxime axetil used in a drug product does not fall within any of these categories.

The fact that GSK's '181 patent is not required to be listed in the Orange Book does not render that patent any less deserving of this statutory protection than patents which are listed therein, nor does it alter the public policy concerns that support the imposition of a 30-month stay of FDA approval of an ANDA in cases where patent litigation is pending based on a patent that is listed in the Orange Book. PDI respectfully submits, therefore, that the 30-month stay of FDA approval for a new drug as to which patent infringement litigation is pending, imposed by 21 U.S.C. § 355(j)(5)(B), should be construed to govern this case.

When Congress passed the Food and Drug Administration (FDA) Modernization Act of 1997 (the "Modernization Act"), PL 101-115, 111 Stat. 2296 (Nov. 21, 1997), it repealed section 507 of the FFDCA, which had proscribed a separate application procedure for antibiotic drugs, and provided that future new drug applications for antibiotics would be governed by the same statutory provisions as other drugs, as set forth in section 505 of the FFDCA. The Modernization Act also provided that certain specified portions of section 505 -- including specified portions of section 505(j), which governs ANDA submissions -- would *not* apply to ANDAs for which the reference listed drug at issue an antibiotic drug that was approved under the now-repealed section 507. 111 Stat. 2296, 2327.

Significantly, Congress did *not* include section 505(j)(5)(B) of the FFDCA on its list of exempted statutory provisions. Section 505(j)(5)(B) imposes a 30-month stay on FDA approval of an ANDA if related patent infringement litigation is pending. If Congress had intended to keep that 30-month stay from applying to ANDAs for generic versions of antibiotics, like CEFTIN®, which had been approved under the old section 507, it could readily have mandated that result by adding section 505(j)(5)(B) to its list of exempted statutory provisions. The fact that Congress did not do so is a telling indication that it intended to afford holders of patents covering antibiotics the same statutory protection that section 505 offers to holders of patents listed in the Orange Book. *E.g.*, *Duncan*, 121 S. Ct. at 2125; *Gozlon-Peretz v. United States*, 498 U.S. 395, 404-05 (1991) (recognizing canon of statutory construction that inclusion of one implies intent to exclude others (*inclusio unius est exclusio alterius*)). Patents covering

antibiotics are no less important, and no less entitled to enforcement of their full statutory term, than patents covering any other listed drugs.<sup>6</sup>

Accordingly, unless a court rules otherwise, a stay should be deemed to be in effect that will preclude any FDA approval of the Ranbaxy or Apotex ANDAs from becoming effective until (1) a court issues a "final order or judgment" regarding the validity and/or infringement of GSK's patent (in which case an approval may become effective as of the date of the final order or judgment (if the patent is found to be invalid and/or not infringed), or as of the date that GSK's patent expires (if the patent is found to be valid and infringed)), or (2) 30 months elapses from the time that GSK filed its complaint against Ranbaxy or Apotex. See 21 U.S.C. § 355(j)(5)(B); 21 C.F.R. § 314.107(b)(3).

**5. FDA Should Initiate Rulemaking Proceedings Pursuant to 5 U.S.C. § 553 to Set Standards for Drugs Containing Different Forms of the Active Ingredient Contained in a Listed Drug.**

FDA also should initiate rulemaking proceedings pursuant to 5 U.S.C. § 553(c) to establish rules of general applicability, general policies, and interpretations of general applicability concerning the use of

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<sup>6</sup> It is important to note that PDI does not suggest that ANDA applicants for generic antibiotic drugs should be asked to assume the burden of identifying applicable antibiotic patents that are not listed in the Orange Book and notifying the holders of those patents of the ANDA filing. *Cf. Abbott Labs. v. Zenith Labs., Inc.*, 934 F. Supp. 925 (D.N.J. 1995) (a pre-Modernization Act case in which the court declined to impose such a burden on ANDA applicants). Rather, PDI urges only that, in cases in which the holder of a patent covering an antibiotic drug actually commences an infringement action against an ANDA applicant before FDA approves the application, the primary legislative intent underlying the 30-month stay – *i.e.*, giving all parties time to litigate their respective patent rights before a proposed new drug product goes to market – will be best served by imposing the stay even though the patent in question covers an antibiotic previously approved under the repealed section 507, and thus is not required to be listed in the Orange Book. *Cf. Ben Venue Labs.*, 146 F. Supp. 2d at 584 (recognizing that Hatch-Waxman Act's certification provisions were enacted for benefit of patent holders, to ensure that patentees have time to pursue pre-marketing litigation).

the ANDA procedure to secure approval of proposed new drugs that differ in form (especially crystalline form) from a listed drug. *See* 5 U.S.C. § 552(a)(1)(D).

As is clear from this Petition, as well as from GSK's Petition, this subject is ripe for agency rulemaking. No specific rules or guidelines exist to direct the course of agency review of ANDAs for such new drugs or to guide the public and the industry in these matters. Each such ANDA has been evaluated as if FDA were exploring *terra nova*. Various rationales for FDA's actions have been given in each instance, but no unequivocal agency interpretation of the FFDCA exists to explain how these ANDAs should be prepared by applicants or how they will be evaluated by the agency.

This has caused much uncertainty, a situation which will only grow worse in the absence of rulemaking. Ranbaxy, for example, in its submissions in connection with its pending ANDA, has taken the position that it is FDA practice to treat all crystalline forms of a chemical compound as the same drug, and that all such forms are therefore eligible for ANDA treatment. *See* November 6, 2000 Ranbaxy Fax Amendment, at B.4.a (Attachment 18). This would be contrary to law. In the absence of a clear Agency statement of its position on this question, however, such confusion is inevitable.

Notice and comment rulemaking is the proper means by which to formulate a legally and scientifically valid approach to this issue. This procedure will give FDA the benefit of the input of all interested parties and the opportunity to solicit the best scientific and legal input for its policy making. The continued *ex parte* review of these ANDAs, individually and under seal, is the worst possible way to develop a legally sound, consistent, and science-based approach to this issue.

FDA should suspend consideration of all ANDAs that seek approval of drugs which differ in form (especially crystalline form) from a listed drug, and initiate rulemaking procedures that will both enable all interested parties to provide input and ultimately provide the public with clear guidance as to how FDA will deal with this class of ANDA submissions.

**C. Environmental Impact**

This petition asks that FDA not approve a pending ANDA for a drug product that does not contain the same active ingredient as the relevant pioneer drug. Because the requested action would not increase the use of the active moiety, the petition is subject to a categorical exclusion from the requirement of an environmental impact assessment. 21 C.F.R. § 25.31(a).

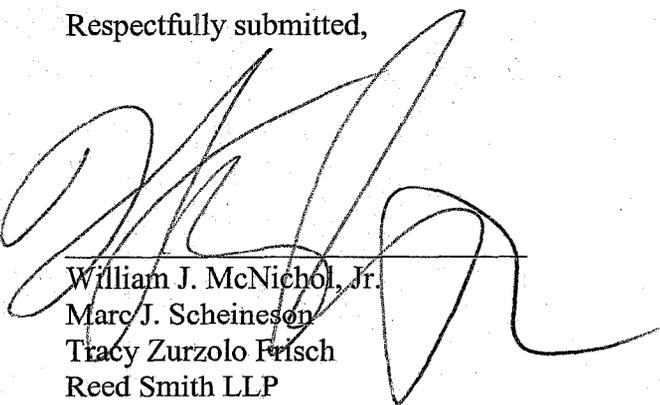
**D. Economic Impact**

Information on the economic impact of this petition will be submitted if requested by the Commissioner.

**E. Certification**

The undersigned certifies 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.

Respectfully submitted,



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Enclosures

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**Exhibits to September 19, 2001 Citizen Petition of  
Professional Detailing, Inc. and LifeCycle Ventures  
Regarding Proposed Generic Cefuroxime Axetil Products**

## INDEX OF EXHIBITS

1. U.S Patent No. 4,562,181
2. Glaxo v. Apotex, Complaint filed on or about 9/22/00
3. Glaxo v. Ranbaxy, Complaint filed on or about 10/20/00
4. Ceftin monograph from *Physician's Desk Reference* (55<sup>th</sup> ed.) (2001)
5. Irena Oszczapowicz, et al., *Esters of Cephalosporins. Part VI. Properties of the  $\beta$ -Form of 1-Acetoxyethyl Ester of Cefuroxime*, Acta Polon. Pharm. - Drug Research Vol. 55 No. 3 (1998)
6. Caroline M. Perry, Rex N. Brogden, *Cefuroxime Axetil: A Review of Its Antibacterial Activity, Pharmacokinetic Properties and Therapeutic Efficacy*, Drugs 1996 Jul; 52(1)
7. The European Agency for the Evaluation of Medicinal Products, Human Medicines Evaluation Unit, Committee for Proprietary Medicinal Products, *Note for Guidance on Development of Pharmaceuticals* (Jan. 28, 1998)
8. April 19, 1999 Letter from Ranbaxy to Office of Generic Drugs
9. Declaration of Shirley Ternyik in Support of Ranbaxy Pharmaceuticals Inc.'s Opposition to Plaintiffs' Motion for a Preliminary Injunction
10. Reply Brief of Defendant-Appellant Ranbaxy Pharmaceuticals, Inc.
11. Nonconfidential Brief of Defendant-Appellant Ranbaxy Pharmaceuticals Inc.
12. European Patent Application No. 0757991 A1 (1995)
13. FDA's Policy Statement for the Development of New Stereoisomeric Drugs (May 1, 1992)
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16. Excerpts from November 9, 2000 Transcript of Deposition of Dipak Chattarj, President of Ranbaxy Pharmaceuticals, Inc.
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