Kirkpatrick & Lockhart LLP

1800 Massachusetts Avenue, NW
Second Floor
Washington, DC 20036-1221
202.778.9000
www.kl.com

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

Re: Docket No. 01P-0428; Comments in Opposition to Professional Detailing, Inc.'s Citizen Petition Contesting FDA Approval of ANDAs for Cefuroxime Axetil Tablets

Dear Sir or Madam:

On behalf of our client, Ranbaxy Laboratories, Ltd. ("Ranbaxy"), we submit these comments in opposition to Professional Detailing, Inc.'s ("PDI") September 20, 2001 Citizen Petition, September 26, 2001 Petition for Stay of Action, and one related supplement (dated October 16, 2001) (collectively referred to hereafter as the "Petitions"). PDI contests the Food and Drug Administration's ("FDA") approval of any generic versions of cefuroxime axetil tablets that would compete with GlaxoSmithKline's ("GSK") Ceftin® and specifically names Ranbaxy's product in its protest. PDI is the sole U.S. distributor of Ceftin®.

In these comments, we will provide evidence that Ranbaxy's abbreviated new drug application ("ANDA") for cefuroxime axetil tablets provides substantial scientific data establishing that Ranbaxy's generic drug is safe, effective, and meets all of the statutory requirements for FDA approval. We also will respond to PDI's unsupportable assertion that Ranbaxy's drug, which contains both the amorphous and crystalline forms of cefuroxime axetil, will not provide the same antibiotic thereapeutic benefit as GSK's Ceftin®.

At the outset, we note that PDI's Petitions are near mirror images of the two petitions and five supplements submitted by GSK on this very same matter. See FDA Docket No.00P-1550. PDI raises no new substantive issues and appears to be part of an orchestrated campaign to further stall the approval of less expensive generic cefuroxime axetil products by requiring FDA to establish two separate dockets for the same issue. In light of uniform positions taken by PDI and GSK, these Ranbaxy Comments contain similar substantive responses to the Comments that Ranbaxy submitted on October 31, 2001, in opposition to the GSK petitions in FDA Docket No. 00P-1550.

PDI argues in its Petitions that FDA lacks the authority to approve an ANDA for cefuroxime axetil tablets that include both the crystalline and amorphous forms of the active ingredient. The motive behind PDI's assertions is crystal clear. GSK holds a patent for the amorphous form of cefuroxime axetil, essentially free of crystalline material (U.S. Patent No. 4,562,181, hereinafter "the '181 patent"). Therefore, PDI and GSK are attacking all generic applications for drugs that

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contain any amount of the crystalline form because such products constitute non-infringing competition to GSK's patented product. PDI attempts to shroud its arguments in terms of law and science, but the Petitions are really about expanding the scope of GSK's patent beyond its legal limits so that GSK and PDI can make as much money as possible before affordable generics enter the market. To that end, PDI has made the following four general objections to the generic versions of the antibiotic.

First, PDI asserts that the generic drug does not contain the "same" active ingredient as Ceftin®, as required by the Federal Food, Drug, and Cosmetic Act ("FDCA"). However, FDA has repeatedly stated that alternative polymorph forms of an active ingredient are the "same" for purposes of meeting the applicable ANDA statutory requirements for approval. Second, PDI claims that the generic drug's labeling differs from that of Ceftin® in that the active ingredient will be described as including the crystalline form of the drug. As described below, this assertion ignores the fact that FDA's regulations and past approvals specifically permit minor labeling differences that accurately describe the form of the generic drug.

Third, PDI contends that FDA should initiate a rulemaking creating standards for all ANDAs involving a drug in an alternate crystalline form from the listed drug. Of course, the FDCA already has established specific parameters by which an ANDA drug is proven safe and effective, which FDA implements through approval requirements in the form of rigorous scientific testing, strict product specifications and validated manufacturing practices, among other things. Finally, PDI alleges that Ranbaxy's ANDA should be subject to the 30 month stay of approval which is applicable to certain ANDAs that include a Paragraph IV patent certification. PDI's claim, however, is contrary to the law and regulations which explicitly state that cefuroxime axetil antibiotic products are exempted from the Paragraph IV certification and the 30-month stay provisions. Because all of PDI's arguments fail, FDA should deny its Petitions.

BACKGROUND

PDI's licensor, GSK, holds a new drug application ("NDA") for the innovator drug, Ceftin®, which allegedly includes only the amorphous form of cefuroxime axetil. GSK has patent protection for cefuroxime axetil in amorphous form, essentially free from crystalline material (the '181 patent). Ranbaxy has developed cefuroxime axetil tablets that contain a specific percentage of the amorphous and crystalline forms of the drug substance (in a proportion of amorphous:crystalline of 85-90:15-10). Ranbaxy submitted an ANDA for its cefuroxime axetil tablets to FDA on April 19, 1999. On August 20, 2001, the U.S. Court of Appeals for the Federal Circuit held that GSK is unlikely to prove that Ranbaxy's drug product infringes GSK's patent, either literally or under the doctrine of equivalents.[1] Following the Federal Circuit's mandate, the District Court for the District of New Jersey vacated the injunction it had

[1] Ranbaxy Pharmaceuticals, Inc. v. Glaxo Group Limited, No. 01-1151 (Fed. Cir. 2001).

previously improperly granted against Ranbaxy.[2] As a result, Ranbaxy is free to market its generic tablets once FDA approves Ranbaxy's ANDA.

With the patent infringement arguments gone, PDI may recognize that blocking FDA approval of cefuroxime axetil ANDAs is its last line of defense against an eroded market share for Ceftin®. It is well-known that, once a generic drug reaches the market, it quickly captures 40 – 75% of the market due to the cost savings that generics offer. With Ceftin® making $280 million per year for GSK,[3] PDI stands to lose millions of dollars per year if Ranbaxy's generic drug acquires even 40% of the market. Fearing this profit loss, PDI joins GSK in submitting eleventh-hour filings designed to delay FDA's approval of generic cefuroxime axetil tablets.

DISCUSSION

A. Ranbaxy's Cefuroxime Axetil Tablets And Ceftin® Contain The Same Active Ingredient Under The Law

In its Petitions, PDI alleges that the active ingredient in Ranbaxy's cefuroxime axetil tablets is not the "same" as the active ingredient in Ceftin® because Ranbaxy's tablets contain a specified percentage of the crystalline form of the drug substance. In making this argument, PDI is asking FDA to arbitrarily reverse an agency policy that has been in existence for over 25 years. The agency has long recognized that an active ingredient of a drug substance can be present in one of several physical forms – whether amorphous or polymorphous (i.e., of crystalline form). Accordingly, the amorphous form found in Ceftin®, and the crystalline form found, in part, in Ranbaxy's product are, from a statutory perspective, two physical forms of the same active ingredient. Ranbaxy has therefore met the applicable statutory requirement that a generic drug contain the "same" active ingredient as the listed drug. Furthermore, despite PDI's mischaracterization of the pleadings in the patent litigation between Ranbaxy and GSK[4] (Citizen Petition at 13-14), Ranbaxy has not, when describing the distinctive traits of its product, stated that the product contains a different active ingredient than Ceftin®.[5] Ranbaxy could not make such a statement because it is false.

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[2] Glaxo Group Limited v. Ranbaxy Pharmaceuticals, Inc., No. 00-5172 (D. N.J. 2001).

[3] According to GSK's website, GSK's U.S. sales of Ceftin exceeded $280 million in 2000.

[4] Glaxo Group Limited v. Ranbaxy Pharmaceuticals, Inc., No. 00-5172 (D. N.J.); Ranbaxy Pharmaceuticals, Inc. v. Glaxo Group Limited, No. 01-1151 (Fed. Cir.).

[5] Ranbaxy also denies that it has taken scientifically inconsistent positions before FDA and the courts. Rather, the science underlying its cefuroxime axetil, which contains amorphous and crystalline forms, has remained the same. The difference is the applicable legal framework. In the patent litigation, the question was whether Ranbaxy's product is so identical to GSK's product that it infringes GSK's patent under U.S. patent laws. In its ANDA submissions, the question is, instead, whether Ranbaxy's product contains the same active ingredient as GSK's product so that it meets the requirements of the FDCA.

1. In the context of ANDAs, FDA has long considered various physical forms of an active moiety to be the "same" active ingredient.

In the context of the statutory requirement that an ANDA product contain the "same" active ingredient as the listed drug, FDA's longstanding policy has been that a product's active ingredient is the same if it contains any physical form of the identical salt or ester of the active moiety.[6] As such, amorphous and polymorphous forms of the same salt or ester are merely different physical forms of the same active moiety and therefore are statutorily the "same." FDA applied this sound reasoning to drug products with different crystalline forms as early as 1987. Specifically, the agency determined that, "[s]ome drug substances exist in several different crystalline forms ('polymorphs'), due to a different arrangement of molecules in the crystal lattice, which thus show distinct differences in their physical properties. The same drug substance may also exist in a noncrystalline (amorphous) form. These various forms differ in their thermodynamic energy content, but not in composition." FDA's "Guideline for Submitting Supporting Documentation in Drug Applications for the Manufacture of Drug Substances" (Feb. 1987), at 33-34 (emphasis added).

FDA recently confirmed in a memo to the U.S. Pharmacopeia ("USP") that "[d]ifferences in physical form, including various solvation states or specific polymorphs, are not part of the understanding of 'sameness' under the Federal Food, Drug, and Cosmetic Act." Memo from Gary J. Buehler, (then) Acting Director, Office of Generic Drugs, FDA, to the Executive Committee of the Council of Experts, United States Pharmacopeia, dated July 10, 2001, at 2 (Exhibit 1). The USP essentially agreed with FDA and determined that a revision to the USP monograph for cefuroxime axetil was appropriate. In particular, the USP published a revised monograph for cefuroxime axteil on June 1, 2001, which became official on September 30, 2001.[7] Previously, the USP monograph was limited to the amorphous form of cefuroxime axetil since the only marketed product, Ceftin®, was labeled as containing cefuroxime axetil in the amorphous form. The monograph now recognizes both the amorphous and crystalline forms. The monograph also describes the substance's crystallinity as follows: "Particles that do not show birefringence or

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Obviously, these two questions cannot be addressed in the same way, would not evaluate "sameness" in a consistent matter, and do not necessarily provide the same answer.

[6] See 54 Fed. Reg. 28,881 (1989).

[7] Given this recent update, the lack of inclusion of the crystalline form in other nations' pharmacopeia's is not surprising. Pharmacopieal monographs are created or revised based on the request of a manufacturer or supplier of the drug substance. Hence, when other national pharmacopeias are petitioned to include the crystalline form of cefuroxime axetil, the monographs will be updated accordingly. Likewise, the inclusion of only the amorphous form of the drug does not signify a "judgment" about whether the two physical forms are the same or not, and certainly does not represent a "consensus" that the crystalline form is inappropriate for use in a drug product, as PDI claims. See Supplement 1 at 2-3.

exhibit extinction positions are amorphous, and particles that show birefringence and exhibit extinction positions are crystalline." None of the other identification parameters or testing specifications in the monograph were changed when the crystalline designation was added. The types of parameters include identification, assay, mobile phase, resolution solution, standard preparation, and chromatographic system, among others. Thus, the monograph now reflects an updated description of the solid state form of the drug substance, while recognizing that the crystalline form already complies with the previous monograph specifications. Like FDA, the USP recognized that a solid state designation does not signify a new active ingredient but, rather, describes in more detail the physical form of the drug substance.[8]

As further evidence of the fact that amorphous and crystalline forms of the same drug are the "same active ingredients," we note that such products can be "therapeutically equivalent" under FDA's therapeutic equivalence policy. In its extensive discussion on therapeutic equivalence determinations, FDA explains:

> Different salts and esters of the same therapeutic moiety are regarded as pharmaceutical alternatives. . . . Anhydrous and hydrated entities, as well as different polymorphs, are considered pharmaceutical equivalents and must meet the same standards and, where necessary, as in the case of ampicillin/ampicillin trihydrate, their equivalence is supported by appropriate bioavailability/bioequivalence studies.

FDA's Approved Drug Products With Therapeutic Equivalence Evaluations ("the Orange Book"), at Preface Section 1.7 (emphasis added). Ranbaxy's cefuroxime axetil, which contains both the amorphous and crystalline forms of the drug substance, is pharmaceutically equivalent and bioequivalent to GSK's cefuroxime axetil in amorphous form. Accordingly, Ranbaxy's drug product is eligible for approval under Section 505(j) of the FDCA.

Additionally, many of the documents cited by PDI in the Petitions actually support the position that cefuroxime axetil (amorphous) and cefuroxime axetil (amorphous plus crystalline) are the same active ingredient. For example, in the preamble to the ANDA Final Rule, referenced on page 12 of PDI's Citizen Petition, FDA specifically stated that the "stereochemistry characteristics and solid state forms" of a generic drug need not be identical to that of the listed drug. 57 Fed. Reg. 17,950, 17,959 (1992). This agency position clearly conflicts with PDI's assertions and confirms that varying solid state forms, such as the amorphous and crystalline forms of cefuroxime axetil, fall within the agency's interpretation of the "same" active

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[8] PDI's licensor, GSK, raised many of the "scientific" issues in PDI's Petitions before the USP Executive Committee, and the issues were carefully considered and debated at a July 30, 2001 hearing where GSK, Ranbaxy and FDA participated. Despite GSK's claims in that forum, the USP determined that the revised monograph, identifying a mere labeling designation, was appropriate and should become official.

ingredient. The ANDA preamble cited by PDI further refutes the firm's arguments by restating FDA's historical position that the agency has discretion to determine what information is necessary to support a "sameness" determination with respect to active ingredients. Id. Perhaps the most troubling aspect of PDI's reference to the ANDA Preamble is the misapplication of FDA's ability to "prescribe additional standards that are material to the ingredient's sameness." Id. This language does not mean that additional standards prohibit a finding of sameness. On the contrary, it means that an active ingredient may meet the same standard for identity even when FDA determines that additional standards must be met for that chemical.

Similarly, PDI quotes Serono Laboratories, Inc. v. Shalala, a case that actually undercuts PDI's argument. In that case, the D.C. Circuit Court of Appeals upheld FDA approval of a generic drug that contained varying isoforms of the active ingredient. In so doing, the court ruled that the statutory term of "same active ingredient" is open to interpretation by FDA and, thus, may be considered by the agency on a case-by-case basis as FDA reviews the particular scientific data of a specific application. Serono, 158 F.3d 1313, 1319 (D.C. Cir. 1998). While PDI unkindly describes this legal theory as a "close enough" standard (see Citizen Petition at 18-20), the courts have called it "proper deference to the expertise of the agency" -- a requirement under administrative law.[9] Specifically, FDA is to be given deference when it is evaluating scientific data within its technical expertise, as in the case of ANDA data.[10]

Ultimately, the Serono court determined that the characterization of an active ingredient does not include only chemical identity (as the Ranbaxy and GSK products have), but also may include clinical identity so long as the data posited to establish sameness is not "insufficient to show that the active ingredients are the same." Id. at 1319. In Ranbaxy's case, its ANDA data establish the chemical identity of cefuroxime axetil via polymorphic form, as well as the clinical identity via a bioequivalence study (described in more detail below).

2. FDA has historically permitted ANDA applicants to use varying physical forms of an active ingredient from that of the listed drug.

PDI is asking FDA to radically depart from its current course. In the past, FDA has repeatedly approved ANDAs for drugs with polymorphic forms that are different from that of the listed

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[9] Citizens to Preserve Overton Park, Inc. v. Volpe, 401 U.S. 402, 416 (1971).

[10] See Zeneca Inc. v. Shalala, 1999 U.S. Dist. LEXIS 12327 (D. Md. 1999) (Aug. 11, 1991), aff'd, 213 F.3d 161 (4th Cir. 2000) (upholding FDA's approval of an ANDA for a drug that contained a different preservative than the listed drug); Schering Corp. v. FDA, 51 F.3d 390, 399 (3d. Cir. 1995) (FDA's "judgments as to what is required to ascertain the safety and efficacy of drugs falls squarely within the ambit of the FDA's expertise and merit deference from us."), cert. denied, 516 U.S. 907 (1995); FPC v. Florida Power & Light Co., 404 U.S. 453 (1972).

drug. Significant examples include cefadroxil, ranitidine hydrochloride and prazosin hydrochloride.

A decade ago, Bristol-Myers Squibb ("BMS") submitted a citizen petition that made many of same arguments PDI is currently advocating. BMS marketed cefadroxil monohydrate capsules, an antibiotic drug product. Zenith Laboratories ("Zenith") filed an ANDA for a generic version of the drug. A monograph for the bulk cefadroxil monohydrate mandated a moisture content for the drug substance of between 4.2 and 6.0 percent. Because Zenith's active ingredient was a "hemihydrate" form of the drug substance, BMS argued that Zenith's drug did not conform to the monograph's moisture content, which was drafted when BMS's monohydrate version was the only available form of the drug. In its citizen petition, BMS asserted that FDA should deny approval of the abbreviated antibiotic drug application submitted by Zenith because the drug was not "the same" as the reference listed drug. See BMS Citizen Petition, dated July 13, 1990 (FDA Docket No. 90P-0240).

As in the present situation, Zenith developed the hemihydrate form in order to provide affordable cefadroxil while simultaneously avoiding infringing on a BMS patent that claimed cefadroxil monohydrate. Because Zenith's product did not infringe BMS's patent, BMS attempted to use the antibiotic monograph to accomplish what its patent could not – prevent generic competition. Similarly, when faced with the reality that Ranbaxy's product does not infringe GSK's patent, PDI seeks to delay FDA's approval of generic cefuroxime axetil tablets by opposing that approval in a citizen petition.

FDA ultimately saw through BMS's unfounded allegation and denied the company's petition. See FDA Docket No. 90P-0240 (Apr. 6, 1992). In reaching its decision, the Agency determined that the anhydrous form of an active ingredient constitutes the "same" active ingredient as the hydrated form, but in a different physical form. In so doing, FDA explained that its position with respect to the therapeutic equivalence of ingredients with different waters of hydration was a long-standing one, dating back at least to 1976 (citing 41 Fed. Reg. 51,087 (1976) and 44 Fed. Reg. 2950 (1979)).

FDA also stated that it had authority to approve an abbreviated application if the product met all of the standards of the antibiotic monograph (except for moisture content specification) and the product was bioequivalent to the listed drug (just as Ranbaxy's product is bioequivalent to Ceftin®). FDA ultimately approved the generic cefadroxil product with labeling that replaced the listed drug's references to "cefadroxil monohydrate" with references to "cefadroxil hemihydrate." The agency subsequently revised the antibiotic monograph to include standards for the identity, strength, quality and purity of cefadroxil hemihydrate, and the cefadroxil monohydrate and cefadroxil hemihydrate products remained equivalent to and substitutable for one another.

PDI, due to its commercial association with GSK, should be well aware of the FDA's scientific position that an active ingredient can be the same even when it arises in distinctive crystalline forms. In November 1994, FDA tentatively approved an ANDA containing a Form 1 crystalline

of ranitidine hydrochloride. In so doing, FDA determined that the Form 1 crystalline was "the same active ingredient" as the listed drug, GSK's Zantac®, which contained a Form 2 crystalline of ranitidine hydrochloride. After several lawsuits alleging patent infringement, Novopharm and Boehringer Ingelheim were permitted to sell FDA-approved equivalent versions of ranitidine hydrochloride containing the Form 1 crystalline.[11]

These historical examples clearly refute PDI's assertion that Ranbaxy's cefuroxime axetil product with an amorphous to crystalline ratio that is different from Ceftin® contains a different active ingredient. In fact, the historical precedents are so closely on point that an FDA denial of Ranbaxy's ANDA on "sameness" grounds would be arbitrary and capricious.

B. The FDCA Permits Ranbaxy's Cefuroxime Axetil Labeling To Reference The Crystalline Form Of The Drug

PDI also argues that the labeling of a generic drug containing the crystalline form of cefuroxime axetil will not be the same as the labeling for Ceftin®, in contravention of the FDCA. In particular, the statute requires an applicant to demonstrate that the proposed labeling for the generic product is the same as the approved labeling for the listed product. 21 U.S.C. § 355(j)(2)(A)(v). Statutory exceptions, however, allow for minor labeling differences. One such exception provides that the ANDA may reflect differences due to the drug's production or distribution by a different manufacturer. Id. FDA interprets this phrase to include variations in "expiration date, *formulation*, bioavailability, or pharmacokinetics, labeling revisions made to comply with current FDA labeling guidelines or other guidance . . . ." 21 CFR § 314.94(a)(8)(iv) (emphasis added). One court in particular has upheld FDA's interpretation on labeling differences, concluding that an ANDA approval was lawful for a generic drug that used a different preservative than the listed drug. See Zeneca, Inc. v. Shalala, 1999 U.S. Dist. LEXIS 12327 (D. Md. Aug. 11, 1991), aff'd, 213 F.3d 161 (4th Cir. 2000). As stated previously, Ranbaxy's cefuroxime axetil drug substance including both amorphous and crystalline forms represents the same active ingredient as Glaxo's amorphous form. Consequently, any labeling changes necessary to reflect the difference in physical form are permissible.

The labeling for Ranbaxy's Cefuroxime Axetil tablets will be the same as the labeling for GSK's Ceftin®, except that the listing of the active ingredient will specify the solid state form of the drug (e.g., "cefuroxime axetil (amorphous __%/crystalline __%)"). This difference is permissible under the exceptions enumerated above. In fact, in the past, FDA has approved ANDAs that incorporated similar differences in the labeling with physical forms that varied from the listed drug.

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[11] See Glaxo Inc. v. Novopharm Ltd., 110 F.3d 1562 (Fed. Cir. 1997); Glaxo Inc. v. Boehringer Ingelheim Corp., 1997 U.S. App. LEXIS 16954 (Fed. Cir. June 4, 1997).

C. The Scientific Data In Ranbaxy's ANDA Establishes That Its Cefuroxime Axetil Tablets Are Safe, Effective And Therapeutically Equivalent To Ceftin®

1. Ranbaxy's bioequivalence data establishes the safety and effectiveness of its generic tablets.

PDI complains that FDA approval of a crystalline-containing cefuroxime axetil product would amount to approval of a less absorbable, inferior, and in-equivalent product. See Citizen Petition at 4. Basically, PDI is attacking the FDA approval process for generic drugs, which is mandated by law. Congress determined that generic drugs must contain the same active ingredient(s) as the innovator drug; be identical in strength, dosage form, and route of administration; have the same use indications; meet the same batch requirements for identity, strength, purity, and quality; and be manufactured under the same strict standards of FDA's good manufacturing practice regulations required for innovator products. In addition, generic drug sponsors must establish that the generic drug is bioequivalent to the innovator drug.

FDA's bioequivalence standard is the product of more than 30 years of intensive scientific studies by hundreds of pharmaceutical scientists and biostatisticians. The bioequivalence criteria has been analyzed and debated many times within FDA and, yet, the agency's study parameters have remained constant. Nevertheless, the brand drug industry has continued to attack FDA's bioequivalence testing requirements – much like PDI's complaint in this forum – prompting FDA to submit letters to the medical establishment to educate them on the scientific validity of bioequivalence testing. For example, FDA has stated that, "[i]n approving a generic drug product, the FDA requires many rigorous tests and procedures to assure that the generic drug is interchangeable with the brand-name drug under all approved indications and conditions of use." January 28, 1998 Letter to Health Care Practitioners from Stuart L. Nightingale, M.D., Associate Commissioner for Health Affairs, FDA. Based on its regular assessment of the quality of generic drug products in the marketplace, FDA explained that there "are no documented examples of a generic product manufactured to meet its approved specifications that could not be used interchangeably with the corresponding brand-name drug." Id.

Furthermore, in correspondence to state pharmacy boards, FDA stated that therapeutically equivalent generic drugs "can be substituted with the full expectation by the patient and physician that they will have the same clinical effect and safety profile as the innovator drug." April 16, 1997 Letter to the National Association of Boards of Pharmacy, from Roger L. Williams, Deputy Center Director for Pharmaceutical Science, CDER, FDA. Thus, PDI's claim that an FDA-approved generic drug could be inferior to its brand counterpart is unfounded.

In keeping with FDA's bioequivalence requirements, Ranbaxy conducted bioequivalence testing on its cefuroxime axetil tablets and established that they are bioequivalent to Ceftin®. 21 U.S.C. § 355(j); 21 C.F.R. part 320. Bioequivalence data establishes that there is no significant difference in the rate and extent of absorption between the generic drug and the listed drug.

Therefore, if an ANDA for cefuroxime axetil contains data that meets FDA's bioequivalence criteria, PDI's alleged concerns about the crystalline form of the drug affecting the product's bioequivalence are refuted. Ranbaxy submitted such bioequivalence data to the agency in its ANDA. Ranbaxy also went a step further and conducted additional bioequivalence testing to confirm bioequivalence throughout its drug product's shelf life. Thus, the inclusion of a specified percentage of crystalline drug substance did not adversely affect the quality of the finished drug product, neither in terms of stability nor bioequivalence.

2. An FDA rulemaking on generic drugs with varying polymorphs would merely duplicate the efforts undertaken during the ANDA review process.

PDI claims that FDA should initate a rulemaking proceeding to set standards for generic drugs that contain a polymorph that varies from the listed drug. PDI cites quality concerns as the basis for this request. Ranbaxy replies that such a rulemaking is unnecessary because the statutory approval process and FDA's ANDA review already ensure that the particulars of a drug product do not affect negatively the safety and effectiveness of the drug. 21 U.S.C. § 355(j); 21 C.F.R. § 314.94. Both safety and effectiveness must be proven by rigorous bioequivalence data and exacting scientific methods. Product consistency is maintained via good manufacturing practice requirements and batch requirements for identity, strength, purity and quality.

In fact, FDA previously has explained that, when approving an ANDA, the agency must assure that satisfactory standards of product quality are met. Specifically, FDA has stated that "[p]art of this assurance consists of drug substance and drug product controls and specifications capable of maintaining these standards for product quality."[12] The agency evaluates each manufacturer's controls for solid state forms, material quality, manufacturing, processing and product characteristics, as well as testing specifications and monitoring capabilities, "regardless of the particular solid state form used in a product."[13] We are confident that FDA's review of Ranbaxy's ANDA and any other ANDA for cefuroxime axetil will be thorough and exacting and will require whatever data is necessary to ensure a safe and effective cefuroxime axetil product in any solid state form, thereby ensuring that if Ranbaxy's product were "inferior" and "damaged goods" as PDI so colorfully asserts, the product would never obtain approval or make it to the market.

Moreover, Ranbaxy has conducted numerous other testing to ensure the quality of various aspects of its product. The company's dissolution data, derived from a two-tier dissolution test, establishes that the percentage of crystalline and amorphous forms in its drug product does not adversely affect the identity, strength, purity, potency or *in vitro* or *in vivo* performance of the drug product. In particular, there is no change in the quality of the product or in the crystallinity

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[12] Memo from Gary J. Buehler, (then) Acting Director, Office of Generic Drugs, FDA, to the Executive Committee of the Council of Experts, United States Pharmacopeia, dated July 10, 2001, at 2.

[13] Id. at 1.

ratio after aging. Ranbaxy has monitored these parameters by infrared spectroscopy and x-ray powder diffraction. The company also has developed specifications for solubility, batch-to-batch consistency, product release, and shelf-life. Of course, Ranbaxy is monitoring all steps of the manufacturing process to ensure that any potential for conversion of amorphous to crystalline, however remote, is controlled. This broad range of testing and specification compliance is more than sufficient to ensure that any product quality issues dreamed up by PDI never come to pass.

Finally, Ranbaxy also has disproved PDI's claim that, within a combined amorphous and crystalline product, there may be an interconversion from the amorphous form to the crystalline form so that, over time, the amorphous/crystalline ratios are not sufficient to assure bioavailability. No such interconversion has occurred, as evidenced by specific testing on Ranbaxy's product. Although several literature references are cited by PDI on this point (see Citizen Petition at 17), none have any bearing on the Ranbaxy formulation presently under FDA review. FDA's scientists in the Office of Generic Drugs have evidence that no such variability exists with respect to Ranbaxy's cefuroxime axetil tablets – not from its formulation properties, manufacturing processes, or storage conditions.

In sum, FDA already requires extensive testing and specification setting for any generic cefuroxime axetil product, pursuant to the applicable statutory framework and FDA's stringent drug approval requirements. As a result, PDI's calls for additional rulemaking standards are superfluous.[14]

D. The 30-Month Stay Provisions Of The Hatch-Waxman Amendments Cannot Be Applied Lawfully To A Cefuroxime Antibiotic Product

PDI's assertions regarding the applicability of the 30-month stay provisions of 21 USC § 355(j)(5)(B) are disingenuous at best and absurd at worst. The FDCA initially established two statutory constructs for the lawful marketing of drugs – one for antibiotics in Section 507 and one for all other drugs in Section 505. The patent listing and patent certification requirements applied to drugs under Section 505, but not to antibiotics. This difference was maintained by the Food and Drug Administration Modernization Act of 1997, Pub. L. No. 105-115, 111 Stat. 2321 ("the Modernization Act") when Section 507 was folded into Section 505. Thus, FDA has no legal authority to apply the 30-month stay provision in Section 505(j)(5)(B) to an antibiotic such as cefuroxime axetil, whether based on "public policy concerns" or otherwise (see Citizen Petition at 25-27).

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[14] Even if FDA were to decide that rulemaking is appropriate on this issue, its application must be prospective after a notice and comment period, pursuant to the Administrative Procedures Act. The retroactive application of such a rulemaking – which is requested by PDI in the form of a stay of approval against all presently-filed ANDAs – is unlawful.

1. The FDCA's 30-month stay provisions historically have not applied to antibiotic drug products.

Under Section 505(j) of the FDCA, codified at 21 U.S.C. § 355(j), a pharmaceutical manufacturer may seek FDA approval to market a generic version of a patented drug by submitting an ANDA.[15] A pharmaceutical manufacturer filing an ANDA under this section must make one of four certifications regarding patents on the drug that is the subject of the ANDA.[16] If the ANDA sponsor files a certification under 21 U.S.C. § 355(j)(2)(A)(vii)(IV) ("a paragraph IV certification"), the patent owner may bring an action against the sponsor for patent infringement under 35 U.S.C. § 271(e)(2)(A).[17] Absent this statutory provision, there is no impediment to ANDA approval based solely on the existence of pending patent litigation. If the patent owner sues within 45 days, that action triggers a statutory 30-month stay during which FDA is prohibited from approving the ANDA. 21 USC § 355(j)(5)(B) (formerly § 355(j)(4)(B) under the pre-1997 version of the FDCA).

At the time these provisions were promulgated as part of the Hatch-Waxman Amendments, manufacturers seeking approval of a generic version of an antibiotic drug, such as cefuroxime axetil, did not file an ANDA under Section 505(j), 21 U.S.C. § 355(j), but instead filed an abbreviated antibiotic drug application ("AADA") under Section 507 of the FDCA, 21 U.S.C. § 357.[18] See 21 U.S.C. § 357 (1997) (repealed) (Exhibit 2). Unlike an ANDA filed under Section 505(j), an AADA filed under Section 507 did not require any patent certification. Moreover, an AADA filed under Section 507 was not subject to 35 U.S.C. § 271(e)(2)(A), and the filing of an AADA did not constitute an act of patent infringement.[19] Thus, in adopting the Hatch-Waxman Amendments, Congress chose not to subject applications seeking approval of antibiotic drugs to the certification provisions of Section 505(j). These are the provisions under

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[15] See Bristol-Myers Squibb Co. v. Royce Labs., Inc., 69 F.3d 1130, 1131 (Fed. Cir. 1995).

[16] See 21 U.S.C. § 355(j)(2)(A)(vii)(I)-(IV); Bristol-Myers, 69 F.3d at 1131.

[17] See Bristol-Myers, 69 F.3d at 1131.

[18] PDI's marketing partner, GSK, is well aware of the historical distinction between antibiotic drugs and other drugs under Sections 505 and 507. In Glaxo, Inc. v. Heckler, 623 F. Supp. 69, 73 (E.D.N.C. 1985), the court rejected GSK's attempt to apply Section 505 of the FDCA to antibiotic drugs. In so doing, the court noted that GSK had lobbied Congress extensively to subject antibiotic drugs to Section 505, but lost the debate. The court also rejected GSK's invitation to "rewrite legislation which Congress expressly considered." Id.

[19] See Brian D. Coggio and Francis D. Cerrito, The Application of the Patent Laws to the Drug Approval Process, 52 Food & Drug L.J. 345, 354 (1997) ("an AADA is not subject to title 35 United States Code Section 271(e)(2), and its filing is not an act of infringement under this section.") (Exhibit 3).

which GSK originally filed its antibiotic drug application for cefuroxime axetil (NDA 050605, approved December 28, 1987).

2. The Modernization Act preserved the distinction between antibiotic drugs and other drugs and, hence, no 30-month stay can be imposed on Ranbaxy's ANDA by the FDA.

The Modernization Act repealed Section 507 of the FDCA and consolidated this provision into Section 505. However, the Modernization Act included a "grandfather" provision and continued to exempt pre-1997 antibiotic drugs from the patent certification provisions of Section 505. As a result, the mere filing of an ANDA for a pre-1997 antibiotic does not automatically constitute an infringing act under the patent infringement provision of 35 U.S.C. § 271(e)(2)(A) and the 30-month stay provision does not apply.

Section 125(b) of the Modernization Act repealed Section 507 of the FFDCA. See Pub. L. No. 105-115, § 125(b). Therefore, an ANDA for an antibiotic drug is now filed under Section 505(j) of the FDCA, 21 U.S.C. § 355(j). However, Section 125(d) of the Modernization Act exempted ANDAs for certain pre-1997 antibiotic drugs from the patent information, patent certification, patent notification and delayed effective date (i.e., 30-month stay) provisions of Section 505. See id. at § 125(d)(2); Donald O. Beers, Generic and Innovator Drugs A Guide to FDA Approval Requirements, § 4.02[I] (5th ed. 1999) (Exhibit 4).[20] The FDA has recognized this exemption for certain pre-1997 antibiotic drugs in its proposed amendments to its own rules to conform to the statute:

> The Modernization Act also exempts certain antibiotic-related drug marketing applications from the marketing exclusivity and patent provisions found in section 505 of the act. Under former section 507 of the act, antibiotic drug applications were not subject to the patent listing and exclusivity provisions in section 505 of the act. Section 125 of the Modernization Act preserves this distinction with an expansive line. Section 125 exempts those applications that contain an antibiotic drug that was the subject of a marketing application received by FDA under former section 507 of the act before November 21, 1997 (prerepeal antibiotic drugs) [now listed by the FDA in 21 C.F.R. § 314.109(b)].

65 Fed. Reg. 3623, 3624 (Jan. 24, 2000) (footnote omitted) (Exhibit 5). FDA explicitly states that pre-1997 antibiotic drugs are not subject to the 30-month stay provision of Section 505(j)(5)(B). Id. at 3624.

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[20] Interestingly, this text is authored by GSK's legal counsel who submitted the Citizen Petition filed by GSK against generic cefuroxime axetil products, FDA Docket No. 00P-1550.

Cefuroxime is one of the antibiotic drugs specifically exempted under the statute and FDA's proposed rule (to be codified at 21 C.F.R. § 314.109(b)). See id. at 3626; FDA "Guidance for Industry and Reviewers: Repeal of § 507 of the Federal Food, Drug, and Cosmetic Act (May 1998) (declaring that "New applications (those received on or after November 21, 1997) under section 505(b) or 505(j) for drugs that contain "old" antibiotics need not include patent information . . . ."). Thus, as interpreted by the FDA, Congress did not intend for the Modernization Act to subject antibiotic drugs containing cefuroxime to the patent certification provisions of Section 505. See 65 Fed. Reg. at 3625-26 (setting forth FDA's administrative view of Congress' intent with respect to the treatment of certain antibiotic drugs).

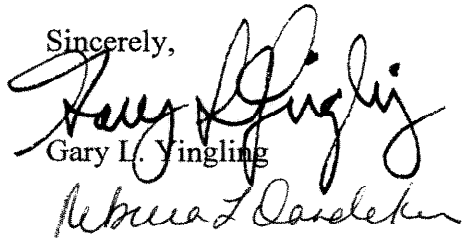
PDI's statement that Congress did not include the 30-month stay provision in its list of exempted statutory provision is incorrect. In reading Section 125(d)(2), PDI apparently does not realize that the statute's citation to Section 505(j)(4)(B) is a reference to the 30-month stay provision. A careful reading of FDA's proposed rule highlights PDI's mistake. FDA explains that "[t]he Modernization Act added a new section 505(j)(3) to the act. This resulted in the renumbering of sections 505(j)(3) through (j)(8) as sections 505(j)(4) through (j)(9), respectively." Id. at 3624.

Since the Modernization Act exempted antibiotic drugs containing cefuroxime from the patent-related provisions found in Section 505, ANDAs for an antibiotic drug containing cefuroxime axetil can be filed without a patent certification paragraph. Thus, Ranbaxy did not make a Paragraph IV certification in its ANDA and the 30-month stay provision was never triggered. As a result, under the law, FDA cannot impose a 30-month stay on the approval of Ranbaxy's ANDA.

CONCLUSION

PDI's Petitions represent nothing more than an anticompetitive tactic to protect its exclusive right to distribute the antibiotic drug, Ceftin®, in the U.S. We maintain that PDI's allegations are unfounded on both the science and the law. We urge FDA to deny PDI's Petitions and approve Ranbaxy's ANDA for cefuroxime axetil tablets, thereby providing access to this safe, effective and affordable antiobiotic to the American public.

Sincerely,



Gary L. Yingling

Rebecca L. Dandeker

cc: Daniel Troy, Chief Counsel
Lynn Whipkey, Office of Chief Counsel
Gary Buehler, Director, Office of Generic Drugs
Cecelia Parise, Office of Generic Drugs