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

Re: Docket No. 00P-1550; Comments in Opposition to GlaxoSmithKline's Citizen Petition Contesting FDA Approval of ANDAs for Cefuroxime Axetil Tablets

Dear Sir or Madam:

On behalf of our client, Ranbaxy Laboratories, Limited ("Ranbaxy"), we submit these comments in opposition to GlaxoSmithKline's ("GSK") September 29, 2000 Citizen Petition, September 29, 2000 Petition for Stay of Action, four related supplements (dated October 30, 2000, December 21, 2000, June 4, 2001, and September 7, 2001), and one comment (dated October 17, 2001) (referred to hereafter as the "Petitions"). GSK's Petitions contest the Food and Drug Administration's ("FDA") approval of any affordable generic versions of cefuroxime axetil tablets that would compete with GSK's drug, Ceftin®. We provide evidence herein 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 of an ANDA. We also counter GSK's assertion that the generic drug will not provide the same antibiotic therapeutic benefit as Ceftin® because Ranbaxy's version contains both the amorphous and crystalline forms of cefuroxime axetil. GSK's arguments are insupportable.

The information provided herein includes an overview of scientific information that Ranbaxy has submitted previously to FDA via its ANDA for cefuroxime axetil tablets. We note for the record that the specific information submitted with Ranbaxy's ANDA is proprietary and contains trade secrets and other confidential information. Nevertheless, we now believe it is appropriate to submit a summary of the information to the docket to publicly demonstrate the invalidity of GSK's claims.

GSK's Petitions assert that FDA cannot approve an ANDA for cefuroxime axetil tablets that include the crystalline form of the active ingredient, in addition to the amorphous form. Since 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") and, thus, generic manufacturers would have to use a non-infringing form of the active drug substance, GSK

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attacks all generic applications that utilize any amount of the crystalline form of the drug. GSK's objections to the generic versions of the antibiotic can be summed up in three general arguments, all of which are unfounded.

First, GSK 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"). Yet, in many cases, FDA has determined that a generic drug meets the statutory approval criteria even though it includes an alternate physical form of the active ingredient. Second, GSK asserts that the generic drug's labeling will not be the same as Ceftin® because the active ingredient will be described as including the crystalline form of the drug. Again, FDA's regulations and past approvals establish that minor labeling differences that accurately describe the form of the generic drug are not a bar to approval. Third, GSK plays on unwarranted fears by claiming that the use of the crystalline form of the drug substance, together with the amorphous form, might negatively affect the antibiotic's therapeutic function. Because FDA is prohibited by law from approving any generic drug whose safety, efficacy, quality or clinical performance are not assured by rigorous scientific testing, strict product specifications, and validated manufacturing practices, GSK's feigned worries are groundless.

Although GSK couches its arguments in terms of the law and science, the true purpose of the Petitions are rooted in economics. GSK hopes to block the approval of any generic competitors and protect its monopoly for Ceftin® so that it can continue to make over $280 million in sales per year. Given the U.S. Government's and the American public's concerns that antibiotics may be in short supply due to the recent anthrax outbreaks, GSK's anti-competitive tactics are especially ill-timed.

BACKGROUND

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 an amorphous form essentially free of crystalline material. 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 show that Ranbaxy's drug product infringes GSK's '181 patent, either literally or under the doctrine of equivalents. Following the Federal Circuit's mandate, the District Court for the District of New Jersey has vacated the injunction it had previously improperly granted against Ranbaxy. As a result, Ranbaxy is free to market its generic tablets once FDA approves Ranbaxy's ANDA.

Having lost its patent infringement arguments in court, GSK likely views blocking FDA approval as 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 over $280 million per year,[1] GSK stands to lose tens of millions of dollars per year if Ranbaxy's generic drug acquires even 40% of the market. Fearing this profit loss, GSK apparently hopes to convince FDA that it should deny approval of any generic version of Ceftin® by its mere volume of filings.

As detailed above, since September 2000, GSK has been flooding FDA with legal documents that oppose the agency's approval of generic cefuroxime axetil tablets. Although the piecemeal submissions may give the impression that GSK could not get its story together in an organized fashion, GSK's strategy of filing an additional opposition paper every few months is actually very effective in delaying competition. Given the fact that FDA wants to make the correct legal and scientific decision on each ANDA it reviews, each new GSK filing causes FDA to pause the ANDA review process and focus instead on GSK's arguments. With the ability to delay the approval process of its competitors (in this case for over one year), and with millions of dollars in profits to be made, it is likely that GSK (or its marketing partners[2]) will continue to submit petitions and supplements monthly or with even greater frequency for the foreseeable future. The only way to gain control over this situation is for FDA to deal with GSK's arguments as what they are – anticompetitive decoys -- and immediately approve Ranbaxy's ANDA for cefuroxime axetil tablets.

DISCUSSION

A. Ranbaxy's Cefuroxime Axetil Tablets Contain The Same Active Ingredient As GSK's Ceftin®

GSK's Petitions allege that Ranbaxy's cefuroxime axetil tablets do not contain the same active ingredient as Ceftin® because Ranbaxy's tablets are made, in part, with the crystalline form of the drug substance. Yet, FDA has acknowledged for at least 25 years that the active ingredient of a drug substance can be present in one of several physical forms – whether amorphous or polymorphous (i.e., of crystalline form). Thus, GSK's amorphous form and Ranbaxy's product which includes crystalline form represent two physical forms of the same active ingredient -- not two separate active ingredients -- and the statutory requirement that a generic drug must contain the same active ingredient as the listed drug has been met.

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

[2] We note that GSK has contracted with Professional Detailing, Inc. ("PDI") to be the exclusive U.S. distributor of Ceftin®. With similar economic interests to protect, therefore, PDI also has submitted a Citizen Petition (September 19, 2001), Petition for Stay (September 25, 2001), and Supplement (October 16, 2001) to FDA, each of which objects to FDA approval of any new or pending ANDA for cefuroxime axetil products. Ranbaxy intends to respond to the PDI petitions under separate cover.

1. FDA interprets "active ingredient" to include the active moiety's various physical forms.

When interpreting the statutory requirement that an ANDA product contain the "same" active ingredient as the listed drug, FDA has determined that a product's active ingredient is the same if it contains any form of the identical salt or ester of the active moiety. See 54 Fed. Reg. 28881 (1989). Amorphous and polymorphous entities are not different salts or esters but, rather, constitute different physical forms of the same active moiety and, thus, are the same under the statutory definition. FDA applied this scientific position to drug products with different crystalline forms as early as 1987. Specifically, FDA 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). Recently, FDA confirmed in a memo to the U.S. Pharmacopeia 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."[3] See Exhibit 1.

Not only do amorphous and crystalline forms of a drug constitute the same active ingredient, but either form also can establish the basis for a therapeutically equivalent generic drug product. In its extensive discussion on therapeutic equivalence determinations, FDA explains that "[d]ifferent 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). In other words, Ranbaxy's cefuroxime axetil including both the amorphous and crystalline forms can be and is, pharmaceutically equivalent and bioequivalent to GSK's cefuroxime axetil in amorphous form and, thus, eligible for approval as an ANDA drug.

Furthermore, the "supporting" documents quoted by GSK, when considered in their entirety, advocate an FDA decision that cefuroxime axetil (amorphous) and cefuroxime axetil (amorphous plus crystalline) represent the same active ingredient. For example, GSK cites the preamble to the ANDA Final Rule. See Citizen Petition at 3-4, Supp. 4 at 3. Yet, in that same preamble,

[3] 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.

FDA specifically rejected the argument that a generic active ingredient must demonstrate the same "stereochemistry characteristics and solid state forms" as the innovator drug. 57 Fed. Reg. 17950, 17959 (1992). Thus, varying solid state forms, such as the amorphous and crystalline forms of cefuroxime axetil, are approvable forms of the same active ingredient. FDA further explained that, when reviewing an ANDA, the Agency has discretion to determine what information is necessary to support a showing that the active ingredient is the same as the listed drug. Id. Moreover, the fact that FDA "may prescribe additional standards that are material to the ingredient's sameness" does not mean that additional standards prohibit a finding of sameness. It means precisely the opposite -- that an active ingredient may meet the same standard for identity even when FDA determines that additional standards must be met for that chemical. We must question whether GSK has deliberately misread the Preamble.

The Draft ICH Guidance and the FDA Draft BACPAC I Guidance referenced by GSK also do little to bolster GSK's arguments. See Citizen Petition at 5. Specifically, the Guidances are intended to be instructive in a general way to FDA as it reviews each new drug application on its own merits. Even so, these Guidances do not suggest that the varying polymorphic forms of a drug substances are different active ingredients.

Finally, GSK quotes Serono Laboratories, Inc. v. Shalala but, 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. Specifically, 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 data of a specific application. Serono, 158 F.3d 1313, 1319 (D.C. Cir. 1998). The 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 approved ANDAs for generic drugs that contain a different physical form than the listed drug.

FDA previously has approved generic drugs with a polymorph form that differed from that of the listed drug. Three well-known examples include cefadroxil, ranitidine hydrochloride and prazosin hydrochloride (equivalent to Minipress®). The cefadroxil case is very similar to the present cefuroxime axetil situation, and the FDA decision in that case clearly refutes GSK's arguments here.

Specifically, Bristol-Myers Squibb (BMS) raised an issue similar to GSK's claim in a 1990 citizen petition. BMS marketed an antibiotic drug, cefadroxil monohydrate capsules. Zenith

Laboratories (Zenith) sought FDA approval for a generic version of cefadroxil monohydrate capsules. An antibiotic monograph for bulk cefadroxil monohydrate set forth identity standards for the drug substance, including a moisture content of between 4.2 and 6.0 percent. BMS alleged that the ingredient referenced in the Zenith application was not a monohydrate and did not conform to the monograph's moisture content. As a monohydrate form of the antibiotic, BMS' cefadroxil contained one molecule of internally-bound water for every molecule of cefadroxil within the crystalline structure, to constitute approximately 4.7 percent of the substance. Zenith's cefadroxil, by contrast, was comprised of mostly adventitious (i.e., surface) rather than internally-bound water and, thus, was a hemihydrate. As such, Zenith's cefadroxil contained a varying crystalline structure from the BMS product. In its citizen petition, BMS asserted that FDA should deny approval of the abbreviated antibiotic drug application[4] submitted by Zenith because the drug was not "the same"[5] as the reference listed drug. See BMS Citizen Petition, dated July 13, 1990 (FDA Docket No. 90P-0240).

In addition to involving a similar scientific inquiry with respect to the polymorphic forms of a drug substance, the Zenith case also parallels the present case in its legal procedural stance. The cefadroxil hemihydrate formulation was utilized by Zenith in an attempt to refrain from infringing a BMS patent on cefadroxil monohydrate, while still providing a generic cefadroxil product to patients. BMS admitted that the Zenith product did not infringe its patent and instead sought to foreclose generic competition by asserting a strict reading of the antibiotic monograph. Likewise, having learned that Ranbaxy's formulation does not infringe GSK's '181 patent, GSK seeks to delay FDA's approval of generic cefuroxime axetil tablets by opposing that approval in a citizen petition.

Ultimately, FDA denied the BMS petition on April 6, 1992. See FDA Docket No. 90P-0240. After a scientific review, FDA determined that the anhydrous form of an active ingredient constitutes the "same" active ingredient as the hydrated form, albeit with a different physical form, for purposes of Sections 505 and 507 of the FDCA. In so doing, FDA explained that its position on 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. 51087 (1976), 44 Fed. Reg.

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[4] In contradiction to GSK's interpretation (see Comment 1 at 2-3), FDA recognized at that time that an abbreviated antibiotic drug application is "regarded as" and "equates with" an ANDA, and is subject to "the same approval procedures." See FDA Letter to Thomas A. Hayes, M.D. from Carl C. Peck, M.D., dated April 6, 1992, at 3 (Docket No. 90P-0240).

[5] In contradiction to GSK's interpretation (see Comment 1 at 2-3), FDA explained that its use of the term "duplicates" is indistinguishable from the term "same" for drug review purposes, and that the requirement for generic versions to provide the same active ingredient applies equally to both antibiotic and drug applications. See FDA Letter to Thomas A. Hayes, M.D. from Carl C. Peck, M.D., dated April 6, 1992, at 3 (Docket No. 90P-0240).

2950 (1979), and the example of ampicillin and ampicillin trihydrate). The agency deduced that the active moiety of both forms was cefadroxil, and that the intended clinical effect of the drug was tied to the cefadroxil and was unaffected by the hydration form.

FDA further concluded 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 GSK's drug). FDA subsequently approved the generic cefadroxil product with labeling that referenced cefadroxil hemihydrate in place of the listed drug references to cefadroxil monohydrate. The agency later revised the antibiotic monograph to set 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.

GSK itself is well aware of the FDA's scientific position that distinctive crystalline forms encompass the same active ingredient. 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. 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).

These similarly-situated examples refute GSK's argument that a cefuroxime axetil product with an amorphous to crystalline ratio that is different from Ceftin® contains a different active ingredient and cannot be approved by FDA. Quite the opposite is true.

3. The U.S. Pharmacopeial monograph recognizes the crystalline form of the cefuroxime axetil drug substance.

Much of GSK's argument that the crystalline form of cefuroxime axetil is not the same active ingredient as the amorphous form relies on the fact that the drug substance monograph for cefuroxime axetil contained in the U.S. Pharmacopeia ("USP") does not include information on the crystalline form of the drug. See Citizen Petition at 3-5, Supp. 3 and Supp. 4. Yet, GSK fails to acknowledge two facts: first, the USP monograph was developed originally by GSK, the manufacturer of the amorphous form of the drug;[6] and second, the USP monograph has been

[6] According to FDA, "[t]he current USP monograph, the labeling for Ceftin®, the former antibiotic monograph for cefuroxime axetil, and the approval of Ceftin® were all based on cefuroxime axetil products containing the amorphous form exclusively." Memo from Gary J. Buehler, (then) Acting

updated to include the crystalline form of the drug. As a result, GSK's stated concerns about the drug's "standard of identity" are moot.

The public has been notified of the USP's intention to include the crystalline form of cefuroxime axetil in the monograph since September 2000, when the USP published the proposed revised monograph. The revised monograph was published in final form on June 1, 2001 and became official on September 30, 2001. See Exhibit 2. The monograph now provides that cefuroxime axetil must be labeled to indicate whether it contains the amorphous and/or crystalline form. The monograph also describes the substance's crystallinity as follows: "Particles that do not show birefringence or 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 merely reflects an updated description of the solid state form of the drug substance while recognizing that the crystalline form already complies with the monograph specifications. As proven above, a solid state designation does not signify a new active ingredient but, rather, describes in more detail the physical form of the drug substance.

As a matter of fact, GSK raised many of the "scientific" issues in its 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.

B. The Labeling For Ranbaxy's Cefuroxime Axetil Tablets Will Be The Same As The Labeling For Ceftin®

GSK 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®. The FDCA 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). However, the statute and regulations have exceptions that allow for minor labeling differences. One such exception provides that the ANDA may reflect differences attributable to the drug's production or distribution by a different manufacturer. Id. The term "production" contemplates differences in manufacturing. FDA's interpretation goes even further, declaring that an ANDA may contain differences in labeling that include variations in "expiration date, formulation, bioavailability, or pharmacokinetics, labeling revisions made to comply with current FDA labeling guidelines or other guidance . . . ." 21 CFR §

Director, Office of Generic Drugs, FDA, to the Executive Committee of the Council of Experts, United States Pharmacopeia, dated July 10, 2001, at 1.

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 (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®, other than two variations: (1) the name of the generic manufacturer will be listed; and (2) the active ingredient will specify the solid state form and be labeled as "cefuroxime axetil (amorphous __%/crystalline __%)." Both of these differences are permissible under the exceptions enumerated above. In sum, a generic label stating that a portion of the active ingredient is present in crystalline form reflects a formulation difference that is permissible under one of the aforementioned regulatory exceptions. Moreover, in the past, FDA has approved ANDAs that incorporated similar differences in the labeling with physical forms that varied from the listed drug.

As noted above, the USP now recognizes both the crystalline and amorphous forms of cefuroxime axetil in the relevant monograph. The revised monograph simply requires that the labeling for a cefuroxime axetil product state whether that chemical appears in the product in amorphous and/or crystalline form. This determination is based on whether the drug substance shows birefringence or not. Because Ranbaxy's product will contain cefuroxime axetil in a polymorphic form, a portion of which will be crystalline, the proposed label will indicate that it contains the crystalline form. Therefore, this label will reflect a statutorily permissible description of a formulation difference.

C. Ranbaxy's ANDA Provides Substantial Scientific Data Establishing That Its Cefuroxime Axetil Tablets Are Safe, Effective And Bioequivalent To Ceftin®

GSK claims that differences in the solid state form of cefuroxime axetil may be significant with respect to safety and effectiveness but cannot reliably be controlled by standard product performance testing. This allegation appears to ignore the entire FDA drug approval process. In the normal course of reviewing any ANDA, FDA is required by law to 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 already has refuted this GSK argument before the USP by explaining 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."[7] 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."[8] 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.

GSK's repeated presumptions that the crystalline form of the drug "may affect" solubility and absorption, causing bioequivalence to be "highly unlikely" are nothing more than interesting academic theory. When applied to an actual drug product in the real world, the hypotheses are proven wrong. As required by the FDCA, 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. Time and again, FDA has confirmed that it "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."[9] Therefore, if an ANDA for cefuroxime axetil contains data that meets FDA's bioequivalence criteria, GSK's alleged concerns about the crystalline form of the drug diminishing its clinical benefit are put to rest. Ranbaxy has submitted such bioequivalence data to the Agency in its ANDA.

Although not required by FDA, Ranbaxy also went a step further and conducted additional bioequivalence testing on its product. To counter GSK's allegation that a predominantly crystalline cefuroxime axetil product might degrade over time, negatively affecting its bioequivalence profile, Ranbaxy conducted an additional bioequivalence study to ensure bioequivalence throughout its drug product's shelf life. The bioequivalence study was conducted using the same batch of the product that was submitted in the ANDA in April 1999. With a shelf-life of 24 months, the bioequivalence of the product was confirmed. Thus, the inclusion of

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[7] 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.

[8] 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 1.

[9] Letter to Health Care Practitioners from Stuart L. Nightingale, M.D., Associate Commissioner for Health Affairs, FDA, dated January 28, 1998.

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, as both have been proved to be unaffected throughout the shelf life of the tablets.

Moreover, Ranbaxy has conducted numerous other testing to ensure the quality of various aspects of its product. The company's dissolution data, 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 ratio after aging. Ranbaxy has monitored these parameters by infrared spectroscopy and x-ray powder diffraction. Ranbaxy 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 GSK never come to pass.

Finally, Ranbaxy also has disproved GSK'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 Dr. Byrn supported his academic theories by relying on GSK's Ceftin® data and on the testing of sample mixtures of various solid state forms, none of the formulations have any bearing on the Ranbaxy formulation presently under FDA review. While GSK tries to startle FDA's lawyers with estimates of extreme variability (see Citizen Petition at 9), 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 addition to Ranbaxy's own testing, the company also hired an independent expert to conduct testing on the GSK cefuroxime axetil (amorphous) and Ranbaxy's cefuroxime axetil (amorphous and crystalline) via differential scanning calorimetry, x-ray powder diffractometry and water uptake. He concluded that the amorphous form of the chemical strongly resists crystallization, even under conditions favoring crystallization (e.g., storage at high temperatures, storage at high relative humidity, after dispersion in water). When included with the crystalline form, as in Ranbaxy's formulation, the amorphous form of the drug still does not transform into crystalline. Details of the expert's testing and conclusions were presented by Ranbaxy during the July 30, 2001 USP hearing at which FDA participated.

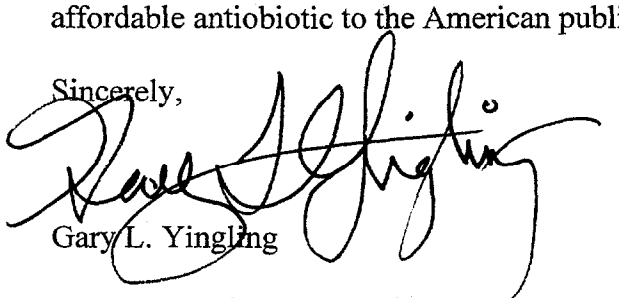
In sum, Ranbaxy already has performed extensive testing and specification setting for its cefuroxime axetil product, pursuant to the applicable statutory framework and FDA's stringent

drug approval requirements. As a result, GSK's calls for additional testing and specification setting are superfluous.

CONCLUSION

GSK's Petitions represent nothing more than an anticompetitive tactic to protect its monopoly for the antibiotic drug, Ceftin®. Despite the avalanche of paper, GSK's allegations are unfounded on both the science and the law. We urge FDA to deny GSK's Petitions and approve Ranbaxy's ANDA for cefuroxime axetil tablets, thereby providing this safe, effective and affordable antiobiotic to the American public.

Sincerely,



Gary L. Yingling

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