



DEPARTMENT OF HEALTH & HUMAN SERVICES

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Food and Drug Administration
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Re: Docket No. 00P-1550/CP1 & PSA1,
Docket No. 01P-0428/CP1 & PSA1

Dear Mr. Beers, Mr. Korn, Mr. McNichol, Mr. Scheineson, and Ms. Frisch:

This responds to two citizen petitions, supplements to the citizen petitions, and accompanying petitions for stay of action whose principal request is that the Food and Drug Administration (FDA) deny the approval of any abbreviated new drug application (ANDA) for a generic cefuroxime axetil product whose active ingredient is wholly or partially in crystalline form.

Glaxo Wellcome Inc., now GlaxoSmithKline (GSK), is the manufacturer of Ceftin Tablets and Ceftin for Oral Suspension, which contain the amorphous form of the active ingredient, cefuroxime axetil. Petition No. 00P-1550/CP1, submitted on September 29, 2000, on behalf of GSK (GSK Petition), requests that FDA deny the approval of any ANDA or application filed under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. 355(b)(2)),¹ for a cefuroxime axetil product whose active ingredient, cefuroxime axetil, is wholly or partially in crystalline form. The petition also requests that if FDA, nonetheless, were to evaluate an ANDA for a generic drug product² that included some portion of crystalline cefuroxime axetil, the Agency should require stringent drug substance and drug product specifications for the solid-state form (including the content of individual polymorphs).

¹ FDA notes that petitioners do not appear to present any additional arguments/issues that are specific to section 505(b)(2) of the Act.

² The petitioners often use the term "generic" to refer to new drug products for which approval is sought in an ANDA submitted under section 505(j) of the Act (21 U.S.C. 355(j)). FDA also frequently uses the term for that purpose in this response to prevent any confusion.

00P-1550

PDN1

Docket Nos. 00P-1550/CP1 & PSA 1 and 01P-0428/CP1 & PSA1

In addition to the GSK Petition, GSK submitted a petition (GSK Petition for Stay) asking FDA to stay the approval of any new or pending application for a product that includes cefuroxime axetil in crystalline form until final resolution of the issues raised in the citizen petition. GSK also requests that, if FDA denies GSK's citizen petition, the stay not expire until a reviewing court has ruled on the correctness of that decision as long as GSK seeks court review within two weeks of its receipt of the adverse decision.

Petition No. 01P-0428/CP1 was submitted on September 21, 2001, on behalf of Professional Detailing, Inc., and its wholly owned affiliate LifeCycle Ventures (collectively, PDI), the United States distributor and marketer of Ceftin products. This petition (PDI Petition) is similar to the GSK Petition. It also asks that FDA deny the approval of any ANDA for a generic drug product containing a mixture of amorphous and crystalline cefuroxime axetil, particularly the pending ANDA submitted by Ranbaxy Laboratories, Inc. (Ranbaxy). The PDI Petition further asks that FDA decline to make effective any approval of the pending ANDAs submitted by Ranbaxy and Apotex, Inc. (Apotex), for a generic drug containing a mixture of amorphous and crystalline cefuroxime axetil until either: (1) 30 months from the date on which GSK commenced a patent infringement action against the ANDA applicant; or (2) 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.³ In addition, the PDI Petition asks FDA to initiate a rulemaking proceeding to establish uniform standards for ANDAs for drug products that contain a different crystalline form and/or different stereoisomeric mixture of an active ingredient than that contained in a reference listed drug.

On September 26, 2001, PDI submitted a petition (PDI Petition for Stay) asking FDA to stay the approval of any ANDA or section 505(b)(2) application, and/or decline to approve any such new or pending application, for a drug product that includes cefuroxime axetil with a different crystalline structure and/or stereoisomeric mixture than that of Ceftin until final resolution of the issues raised in the PDI Petition. PDI also requests that, if FDA denies PDI's citizen petition, the stay not expire until a reviewing court has ruled on the correctness of that decision as long as PDI seeks court review within two weeks of its receipt of the adverse decision.

I. SUMMARY OF FDA'S DECISION

FDA reviewed the GSK Petition and GSK Petition for Stay, the PDI Petition and PDI Petition for Stay, the supplements to the GSK Petition submitted on October 30, 2000, and June 4, September 10, September 26, October 17, and November 7, 2001, the supplements to the PDI Petition submitted on October 16 and December 3, 2001, and the comments submitted by Ranbaxy on October 31 and November 2, 2001. FDA denies both citizen petitions and both petitions for stay.

FDA denies both citizen petitions for several reasons. FDA will approve a generic drug product if, among other things, the active ingredient in the generic drug product is the "same" as the

³ GSK initiated patent infringement actions against Apotex and Ranbaxy on or about September 22, 2000, and October 20, 2000, respectively (PDI Petition at 8).

active ingredient in the reference listed drug. Generally, a difference in the physical form of an active ingredient in the generic drug product from the physical form of the active ingredient in the reference listed drug, including a difference in the crystalline structure of the active ingredient, does not bar the approval of a proposed generic drug product. Specifically, in FDA's view, Ranbaxy has met its burden of providing sufficient information in its ANDA to show that the partially crystalline cefuroxime axetil in its generic cefuroxime axetil drug product is the "same" as the amorphous cefuroxime axetil in the reference listed drug, Ceftin Tablets. That is, Ranbaxy's generic cefuroxime axetil drug product contains the "same" active ingredient as the active ingredient in GSK's Ceftin Tablets. FDA's decision to approve Ranbaxy's generic drug product is consistent with FDA's previous approval decisions and policies.

A generic drug product must be the "same" as the reference listed drug product. Ranbaxy's generic cefuroxime axetil drug product is the "same" as GSK's cefuroxime axetil drug product, Ceftin Tablets. Ranbaxy's generic cefuroxime axetil drug product also has the "same" labeling as Ceftin except for differences permitted by law. FDA's review of any ANDA includes ensuring that the ANDA applicant has the appropriate controls in place with respect to the drug substance and drug product. In FDA's view, Ranbaxy has appropriate controls with respect to the drug substance and the drug product.

FDA also concludes that a thirty-month stay of the approval of ANDAs for generic cefuroxime axetil products is not required by the Act, and such a stay is not appropriate. Furthermore, FDA's view is that the Act, existing regulations, preamble statements, and the FDA publication *Approved Drug Products With Therapeutic Equivalence Evaluations (Orange Book)* provide an adequate basis to guide the Agency's decisionmaking on ANDAs seeking approval of a generic drug product whose active ingredient has a different physical form than the active ingredient in the reference listed drug.

FDA denies both petitions for stay because the petitioners have not demonstrated that they have met all the provisions mandating a stay. Specifically, the petitioners have not demonstrated sound public policy grounds supporting a stay; petitioners also have not shown that the delay resulting from a stay is not outweighed by public health or other public interests.

II. BACKGROUND

A. Cefuroxime Axetil

Cefuroxime axetil is a broad-spectrum cephalosporin antibiotic. Cefuroxime axetil is comprised of two diastereoisomers,⁴ isomers A and B, in a fixed ratio. Currently, the ratio of cefuroxime

⁴ Stereoisomers are molecules that have the same constitution (i.e., molecular formula and chemical connectivity) but differ in the spatial orientation of their atoms. Diastereoisomers are stereoisomers whose molecules are not mirror images of each other and may have different chemical properties. FDA notes cefuroxime axetil itself is comprised of two diastereoisomers, isomers A and B, in fixed ratio within a certain range.

axetil diastereoisomer A to the sum of the cefuroxime axetil diastereoisomers A and B must be between 0.48 and 0.55.⁵

In its cefuroxime axetil products (Ceftin Tablets and Ceftin for Oral Suspension), GSK uses cefuroxime axetil that has a diastereoisomer ratio within this range, and it uses amorphous cefuroxime axetil.⁶ Ranbaxy, in its generic cefuroxime axetil tablets, uses cefuroxime axetil that also has a diastereoisomer ratio within this range, and it uses, in part, crystalline cefuroxime axetil. In sum, GSK and Ranbaxy use different physical forms of the same active ingredient.

FDA notes that pharmaceutical solids can exist in different physical forms. Amorphous solids consist of disordered arrangements of molecules and do not possess a distinguishable crystal lattice.⁷ Different crystalline forms of the same active ingredient are known as "polymorphs." "Polymorphism" is often characterized as the ability of a drug substance⁸ to exist as two or more crystalline phases that have different arrangements and/or conformations of the molecules in the crystal lattice.⁹ An "amorphous" form of a drug substance is not crystalline, but amorphous forms are sometimes regarded as polymorphs.¹⁰ Different polymorphs or amorphous forms of a drug substance still have the same primary chemical structure regardless of the physical form; they also have the same chemical identity.¹¹

⁵ *United States Pharmacopeia 24/National Formulary 19 (USP 24)* at 355 (1999).

⁶ The labeling for the Ceftin products describes the active ingredient as being "in the amorphous form." When FDA approved the Ceftin products, the then-effective antibiotic bulk drug monograph for cefuroxime axetil described the drug as "amorphous and not crystalline" (21 CFR 442.19(a)(iii)). In a direct final rule published in the *Federal Register* on May 12, 1998 (63 FR 26066), and effective September 24, 1998, FDA repealed all antibiotic monographs in accordance with section 125 of the Food and Drug Administration Modernization Act of 1997 (FDAMA), Public Law 105-115 (1997). Section 125 of FDAMA repealed section 507 of the Act, which was the section under which the Agency certified antibiotics.

⁷ See David J. Grant, "Theory and Origin of Polymorphism," in *Polymorphism in Pharmaceutical Solids: Drugs and the Pharmaceutical Sciences*, Vol. 95, at 8 (Marcel Dekker, Inc., 1999) [hereinafter *Polymorphism in Pharmaceutical Solids*].

⁸ The terms "drug substance" and "active ingredient" are interchangeable for the purposes of this citizen petition response.

⁹ *Polymorphism in Pharmaceutical Solids* at 1-2.

¹⁰ *Id.* at 8.

¹¹ FDA notes that a given chemical compound may be described by a series of symbols that represent the actual number and kind of atoms, i.e., the molecular formula. The particular spatial arrangement of this specified number and kind of atoms is called the structural formula. The term chemical structure is commonly used to encompass both molecular and structural information, i.e. the chemical structure of a given compound may be described as a series of symbols that represent the number, kind, and spatial arrangement of atoms, according to certain conventions. Chemical compounds may exist in many physical forms. Examples of different physical forms include different phases (solid, liquid, and gas) and different polymorphs. Although different forms may have very different appearances and physical characteristics, they consist of the same primary chemical structure.

B. USP Monographs Generally

Monographs that appear in the *United States Pharmacopeia (USP)* are relevant to FDA's consideration of ANDAs for generic drug products. The *USP*, which is published by the United States Pharmacopeial Convention (known informally as "the USP"), contains monographs on drug substances and drug products. These monographs, which are developed by committees of experts in the scientific and medical community, contain generally accepted specifications and standards for drug substances and drug products on matters such as identification, dissolution, and assay.¹² FDA often participates in the USP's decisionmaking process with respect to the development and revision of drug substance and drug product monographs because, among other things, these monographs are relevant to FDA's review of ANDAs for generic drug products.

Although the USP's monographs are relevant to FDA's ANDA (and NDA) review process, only FDA has the authority to review and approve ANDAs (and NDAs). Some FDA regulations acknowledge that satisfaction of *USP* standards may satisfy certain regulatory requirements with respect to the drug substance and drug product.¹³

C. USP Cefuroxime Axetil Monograph¹⁴

Until recently, the *USP* monograph for the drug substance, cefuroxime axetil, specified the amorphous form of the drug substance.¹⁵ The aforementioned *USP* monograph was developed based on information pertaining to cefuroxime axetil having the amorphous form exclusively. The *USP*, in its "Commentary" section, mentions that "[f]or a number of years the *USP* monograph specifically required that [cefuroxime axetil] should be in amorphous form because that was the characteristic of the originally approved and marketed product."¹⁶

¹² FDA notes that, in lay terms, identification, dissolution, and assay specifications are generally used to verify the identity of the material being examined, to determine the rate of drug release from a dosage form, and to determine the amount or purity of a drug substance in a formulation, respectively.

¹³ See, e.g., 21 CFR 314.94(a)(9) (referencing § 314.50(d)(1), which provides, among other things, that reference to the current edition of the *USP* may satisfy relevant requirements in § 314.50(d)(1)).

¹⁴ FDA notes that the *United States Pharmacopeia 25/National Formulary 20 (USP 25)* is the USP's current official compendium, but to place the arguments in proper context many of the citations in this response refer to the *USP 24*. *USP 24* became "official" on January 1, 2001. *USP 25* became "official" on January 1, 2002. However, because of differences in publication schedules, *Pharmacopeial Forum* 27(6), Nov.-Dec. 2001, contains the most current display of this particular monograph. FDA notes that the USP uses the term "official" to indicate the effective date of *USP* volumes. The USP also uses the term "official" to refer to the final status of its monographs. FDA notes that, in this citizen petition response, the term "final" is used instead of the term "official" when referring to the final status of *USP* monographs.

¹⁵ *USP 24* at 355-56.

¹⁶ See *Supplement to USP 24* at 3188 (August 1, 2001).

However, in the September-October 2000 Pharmacopeial Forum, the USP published proposed modifications to the cefuroxime axetil monograph that would modify the specification of the polymorphic form of the drug substance (thereby recognizing both amorphous and crystalline forms of the drug substance); the proposed modification would specify that the labeling indicate whether the drug substance is amorphous or crystalline.¹⁷ On March 6, 2001, the USP announced that the revised monograph would be published in June 2001 and would become final on August 1, 2001.¹⁸

On May 25, 2001, GSK filed an appeal of the decision to revise the monograph. Based on information FDA obtained in its review of Ranbaxy's proposed cefuroxime axetil drug product, the Agency expressed its support for the proposed modification of the specification to recognize the crystalline form of cefuroxime axetil.¹⁹ After reviewing scientific information (including information submitted by GSK and Ranbaxy), the USP announced, on August 14, 2001, that the decision to revise the monograph had been upheld and that the changes to the monograph would become final on September 30, 2001.²⁰ The USP also announced that it had approved a change to the cefuroxime axetil tablets monograph²¹ to add a labeling statement providing information on the percentage of crystalline and/or amorphous forms of cefuroxime axetil in the dosage form.²² These monograph revisions became final on September 30, 2001.

It is important to note that this change in the *USP* monograph (to recognize the crystalline form of cefuroxime axetil) obviates the need to address certain issues raised in the GSK Petition. Specifically, GSK maintains (GSK Petition at 6) that a generic drug product that contains cefuroxime axetil wholly or partially in crystalline form would not meet the standards for identity described in the *USP* monograph, and it would have to bear labeling that differed from Ceftin with respect to the name of the drug; GSK maintains that such a product would be misbranded. The need to address this issue was obviated by the final revisions to the *USP* cefuroxime axetil monograph to recognize both the crystalline form and the amorphous form of cefuroxime axetil. Accordingly, a drug product whose active ingredient is cefuroxime axetil that is wholly or partially in crystalline form would comply with the revised monograph (with respect to the name and description of the drug substance).

¹⁷ In-Process Revision, *Pharmacopeial Forum* 26(5), Sept.-Oct. 2000, at 1277.

¹⁸ Letter from Joseph G. Valentino, Senior Vice President, Secretary, and General Counsel, USP, to Yana Mille, Chief, Compensial Operations Staff, Office of Pharmaceutical Science, Center for Drug Evaluation and Research, FDA, March 6, 2001.

¹⁹ Memorandum from Gary J. Buehler, Acting Director, Office of Generic Drugs, to the Executive Committee of the Council of Experts, USP, July 10, 2001.

²⁰ Bulletin Announcing Revision to *USP 24/NF 19*, August 14, 2001 (Revision Bulletin).

²¹ *USP 24* at 356-57.

²² Revision Bulletin.

III. RESPONSE TO GSK PETITION

Following is a discussion of issues raised in the GSK Petition and FDA's responses to those issues. Although the arguments advanced in the PDI Petition are similar to those advanced in the GSK Petition, the PDI Petition raises additional arguments that are addressed in Section VI below.²³

A. Approval of a Generic Drug Product Containing Cefuroxime Axetil in Crystalline Form Would Not Be Unlawful

GSK maintains that approval of an ANDA for a product formulated wholly or partially with crystalline cefuroxime axetil would violate federal law for two reasons. Specifically, GSK maintains that such a generic drug product would not meet the requirements of the Act that a generic drug product (1) contain the same active ingredient and (2) have the same labeling as the reference listed drug. As explained below, FDA approval of a generic drug product containing cefuroxime axetil wholly or partially in crystalline form would not violate the Act or FDA regulations.

1. Generally, a Cefuroxime Axetil Drug Product Whose Active Ingredient Is Wholly or Partially in Crystalline Form Has the Same Active Ingredient as a Cefuroxime Axetil Drug Product Whose Active Ingredient Is in Amorphous Form If the Same Standards of Identity Are Met

GSK contends (GSK Petition at 3) that cefuroxime axetil wholly or partially in crystalline form is not the "same" active ingredient as amorphous cefuroxime axetil within the meaning of section 505(j)(2)(A)(ii)(I) of the Act and 21 CFR 314.92(a)(1).

A difference in the physical form of an active ingredient in a generic drug product from the physical form of the active ingredient in the reference listed drug, including a difference in the crystalline structure of the active ingredient, does not bar the approval of a proposed generic drug product.

a. FDA's regulatory scheme for determining whether the proposed generic drug product and reference listed drug contain the same active ingredient

Section 505(j)(2)(A)(ii)(I) of the Act specifies that an ANDA must contain information to show that the active ingredient is the "same" as that of the listed drug to which the ANDA refers (the "reference listed drug"). Under section 505(j)(4)(C)(i), FDA may refuse to approve an ANDA referencing a listed drug that has only one active ingredient if the ANDA contains insufficient information to show that the active ingredient is the "same" as that of the reference listed drug. Thus, the ANDA applicant has the burden to provide sufficient information to show that the

²³ The PDI Petition incorporates by reference the GSK Petition and its accompanying exhibits and supplements, as well as the evidence cited therein (PDI Petition at 6, footnote 2). The GSK Petition incorporates by reference the documents submitted in support of PDI's petition (September 26, 2001, letter from Donald O. Beers).

active ingredient in the proposed generic drug product is the "same" as the active ingredient in the reference listed drug.

These statutory provisions do not describe the type of information that an ANDA applicant must submit to demonstrate that the active ingredient in its proposed generic drug product is the same as the active ingredient in the reference listed drug; nor do they describe the type of information on which FDA may rely in making its determination as to whether the ANDA applicant has met its burden to provide sufficient information to show the active ingredient in the proposed generic drug product is the same as the active ingredient in the reference listed drug. These statutory provisions provide FDA with a broad grant of discretion with respect to the information that the Agency may consider in making a finding on "sameness."²⁴

FDA regulations implementing section 505(j) of the Act provide that an ANDA is suitable for consideration and approval if the proposed generic drug product is the "same as" the reference listed drug (21 CFR 314.92(a)(1)). Specifically, § 314.92(a)(1) states that the term "same as" means, among other things, "identical in active ingredient(s)." In its 1992 final rule on ANDA regulations, FDA stated that it will "consider an active ingredient [in a generic drug product] to be the same as that of the reference listed drug if it meets the same standards for identity."²⁵

In the 1992 final rule, FDA specifically rejected a proposal that would have required an ANDA applicant to demonstrate that the active ingredient in its proposed generic drug product and the active ingredient in the reference listed drug "exhibit the same physical and chemical characteristics, that no additional residues or impurities can result from the different manufacture or synthesis process[,] and that the stereochemistry characteristics and solid state forms of the drug have not been altered."²⁶

Instead, FDA adopted a more flexible approach stating that it will, as mentioned above, consider an active ingredient in a generic drug product to be the same as the active ingredient in the reference listed drug if it meets the same standards for identity.²⁷ FDA stated that, in most cases, the standards for identity are described in the *USP*, although the Agency might prescribe "additional standards that are material to the ingredient's sameness."²⁸ Standards for identity

²⁴ See generally *Serono Laboratories, Inc. v. Shalala*, 158 F.3d 1313 (D.C. Cir. 1998).

²⁵ 57 Fed. Reg. 17950 at 17959 (April 28, 1992).

²⁶ *Id.* at 17958-59.

²⁷ *Id.* at 17959.

²⁸ *Id.* The preamble states that, "[f]or example, for some drug products, standards for crystalline structure or stereoisomeric mixture may be required" (*id.*). Accordingly, in a different situation, if FDA's experience and expertise in reviewing multiple ANDAs resulted in sufficient evidence that crystalline structure or stereoisomeric mixture made a difference with respect to a particular active ingredient's sameness, the Agency might prescribe additional standards regarding such properties.

generally refer to the tests/specifications (i.e., relating to identification or assay) described in the *USP* with respect to a particular drug substance or drug product.

b. FDA's regulatory scheme and cefuroxime axetil

Given this regulatory scheme, and FDA's current scientific knowledge of polymorphs and amorphous forms, FDA could approve an ANDA for a proposed generic drug product containing cefuroxime axetil that has a different physical form (wholly or partially crystalline form) than the cefuroxime axetil (amorphous form) in the reference listed drug, Ceftin. Consistent with FDA's general policy noted above, FDA considers the (wholly or partially) crystalline cefuroxime axetil in any proposed generic cefuroxime axetil drug product to be the "same" as the amorphous cefuroxime axetil in Ceftin, if the same standards for identity are met. In most cases, as mentioned above, these standards for identity are described in the *USP*, although FDA may prescribe additional standards that are material to the active ingredient's sameness.

After evaluating the available scientific evidence (as discussed in more detail in the next section), FDA concludes that different physical forms of cefuroxime axetil do not affect the identity of cefuroxime axetil, and FDA has determined that no additional standards, including standards on crystalline structure or stereoisomeric mixture, are necessary with respect to establishing the sameness of cefuroxime axetil in a generic cefuroxime axetil tablet product.

Therefore, if an ANDA applicant provides sufficient information to show that the cefuroxime axetil (in wholly or partially crystalline form) in its proposed generic cefuroxime axetil drug product meets the standards for identity in the *USP*, FDA will consider the proposed generic drug product to contain the "same" active ingredient as the reference listed drug, Ceftin. The standards for identity with respect to cefuroxime axetil include tests/specifications relating to identification, crystallinity, diastereoisomer ratio, and assay. Ranbaxy's ANDA for its generic cefuroxime axetil tablets shows that the cefuroxime axetil in its generic drug product meets the standards for identity described in the *USP*. Thus, FDA considers Ranbaxy's partially crystalline form of cefuroxime axetil to be the same active ingredient as the amorphous form of cefuroxime axetil in GSK's Ceftin.

PDI maintains (PDI Petition at 21) that the USP's decision to revise the cefuroxime axetil monograph does not change the fact that a proposed generic product containing a mixture of amorphous and crystalline cefuroxime axetil does not contain the same active ingredient as Ceftin.

The USP's decision to revise the monograph is consistent with the USP's typical approach in that its monographs generally do not address differences in physical form unless and until a specific issue is brought to the USP's attention.²⁹ As mentioned previously, the *USP*, in its

²⁹ Similarly, when FDA established the now-repealed antibiotic monographs, the Agency tended to rely on the information provided by the manufacturer of the innovator drug — generally the same information that was provided to the USP. Therefore, the fact that the FDA cefuroxime axetil bulk drug monograph that formerly appeared in § 442.19 specified amorphous cefuroxime axetil does not constitute an FDA determination that amorphous cefuroxime axetil is a different active ingredient than other physical forms of cefuroxime axetil. As may

"Commentary" section, mentions that "[f]or a number of years the USP monograph specifically required that [cefuroxime axetil] should be in amorphous form because that was the characteristic of the originally approved and marketed product."³⁰ The USP's modification to the specification of the polymorphic form, which occurred after careful consideration of the available scientific evidence (including information submitted by GSK), reflects the USP's understanding that the specification of the physical form may be different and does not affect the identity of the cefuroxime axetil drug substance.

Other evidence that physical form does not play a significant role in the USP's designation of drug substances is found in *USP* General Chapter <197> Spectrophotometric Identification Tests.³¹ One of the common spectrophotometric identity tests involves comparing the infrared absorption spectrum of a test material to that obtained concomitantly for the corresponding *USP* reference standard. The *USP* notes that differences in spectra may be attributed to differences in polymorphic form. In such cases, it is acceptable, unless otherwise stated in the monograph, to convert the test material and reference standard to a common physical form to compare the identity. That is, equal amounts of the test material and reference standard are dissolved in equal volumes of the same suitable solvent; the solution is evaporated to dryness in similar containers under identical conditions, and spectra are obtained of the residues. Formulation of true solutions of the test material and the reference standard renders irrelevant the initial physical form of each. The use of identical conditions to recover the test material and reference standard from solution results in recovering the test material and reference standard in the same physical form. Accordingly, since this test specifically requires the preparation of a common physical form before identity comparison, the physical form of the drug substance is not critical to defining its identity.

PDI states (PDI Petition at 21) that the *USP* manufacturing standard and the FDA standard for ANDA approval are not the same, and it claims that FDA has expressly recognized that *USP* monographs merely establish a minimum threshold for drug identity (id., citing 57 Fed. Reg. 17950 at 17959).

As mentioned previously, FDA concurred with the USP's decision to change the cefuroxime axetil monographs to recognize both the crystalline and amorphous forms of the drug substance.³² Also, in the preamble to the final rule on ANDAs, FDA states that, in reviewing and approving an ANDA, it will consider an active ingredient to be the same as that of the reference listed drug if it meets the same standards for identity. FDA added that "[i]n most cases," these standards are described in the *USP*.³³ FDA concludes that meeting *USP* standards

occur under the *USP* monograph system, a company could have petitioned FDA to revise an antibiotic bulk drug monograph to allow for different polymorphs of the same active ingredient.

³⁰ See *Supplement to USP 24* at 3188.

³¹ *USP 24* at 1855-56; see also *USP 25* at 1920.

³² Memorandum from Gary J. Buehler, Acting Director, Office of Generic Drugs, to the Executive Committee of the Council of Experts, USP, July 10, 2001.

³³ 57 Fed. Reg. 17950 at 17959.

is appropriate for establishing the "sameness" of the active ingredient in cefuroxime axetil tablets. Although the preamble acknowledges that additional standards might be appropriate "in some cases" if the additional standards are "material to the ingredient's sameness," FDA concludes, based on the information it obtained in the course of its ANDA review process for proposed cefuroxime axetil tablets, that no additional standards, including any concerning physical form, are necessary to ensure the sameness of the active ingredient in cefuroxime axetil tablets.

c. FDA's scientific knowledge of polymorphs and amorphous forms of drug substances supports this decision; this knowledge, which is gleaned from FDA's experience and expertise, is reflected in FDA's policies

For a generic drug product to be regarded as having the same active ingredient under § 314.92(a)(1), the drug substance in a proposed generic drug product need not have the same physical form as the drug substance in the reference listed drug. FDA states in the *Orange Book* that the Agency considers drug products containing different polymorphs of the same drug substance, as well as products containing anhydrous and hydrated versions of the same substance, to be pharmaceutically equivalent.³⁴ The *Orange Book* describes pharmaceutical equivalents as, among other things, containing the same active ingredient(s). Therefore, FDA regards different polymorphs of a drug substance as the same active ingredient.

As mentioned above, different polymorphs or amorphous forms of a drug substance still have the same primary chemical structure regardless of the physical form; they also have the same chemical identity.

Further evidence that FDA regards different polymorphs of a drug substance as the same active ingredient appears in the Agency's *Guideline for Submitting Supporting Documentation in Drug Applications for the Manufacture of Drug Substances*, issued February 1987. In a section discussing the relationship of solid-state drug substance forms to bioavailability, the Guideline notes the following:

Some 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*.³⁵

³⁴ *Orange Book* (21st ed.) at xvi (2001).

³⁵ *Guideline for Submitting Supporting Documentation in Drug Applications for the Manufacture of Drug Substances* (February 1987) at 46 (emphasis added).

As the Guideline points out, the polymorphic form of a drug substance can affect the dissolution and bioavailability of drug products.³⁶ Thus, it is possible that a difference in physical form of the active ingredients might prevent a proposed generic drug from being bioequivalent to the reference listed drug (thus barring approval of the ANDA). However, this difference in bioequivalence would not mean that the generic and reference listed drug products contained different active ingredients; it would mean that the *drug products* would not be the "same." In this sense, differences in the physical form of an active ingredient are similar to differences in the particle size of a drug substance, which do not result in differences in the identity of active ingredients but which can produce differences in solubility rate, dissolution behavior, and bioavailability.

GSK cites (GSK Petition at 5) a draft guidance issued by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and an FDA draft guidance as support for its view that the physical form of cefuroxime axetil is essential to the sameness determination. The ICH draft guidance *Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances (ICH Q6A)*³⁷ identifies four appropriate methods for characterizing solid-state forms of drug substances. GSK contends that amorphous and crystalline forms tend to differ in each one of the tests. GSK also states that FDA's draft guidance entitled *BACPAC I: Intermediates in Drug Substance Synthesis; Bulk Actives Postapproval Changes: Chemistry, Manufacturing, and Controls Documentation* (November 1998) (at 7) states that only two physical properties of a drug substance, morphic form and particle size, are considered critical for evaluation of equivalence. *BACPAC I*, which FDA finalized in February 2001,³⁸ states the conditions under which the physical properties of a drug substance will be considered equivalent after a given postapproval change.

ICH Q6A is not intended to preclude or eliminate changes in drug products. Rather, its purpose is to highlight areas of change where additional data should be developed to justify certain differences. The same is true of FDA's *BACPAC I* guidance. Contrary to GSK's claim, these guidances do not support the proposition that a generic cefuroxime axetil drug product can be considered the "same" as Ceftin only if it has the totally amorphous form of the active ingredient. If a polymorph displays different properties such as melting point, solubility, and stability, these characteristics could ultimately have an impact on the approval of an ANDA for a proposed generic *drug product*. These characteristics could ultimately affect the approval because the approval is based not only on whether the active ingredient in the proposed generic drug product is the "same" as the active ingredient in the reference listed drug, but also on whether the proposed generic *drug product* is the same as the reference listed drug. FDA will approve a generic drug product if the ANDA applicant provides, among other things, sufficient information

³⁶ Id. at 44, 47-48.

³⁷ FDA published this draft guidance in the November 25, 1997, issue of the *Federal Register* (62 Fed. Reg. 62890). On December 29, 2000 (65 Fed. Reg. 83041), FDA published the final *ICH Q6A* guidance.

³⁸ 66 Fed. Reg. 10699 (February 16, 2001).

to show that the *generic drug product* is the "same" as the reference listed drug. However, if the active ingredient of a proposed generic drug product were to have a different polymorphic form than the active ingredient in the reference listed drug, and this difference affected the behavior or certain characteristics of the drug product, then FDA might not approve the generic drug product, despite the fact that the proposed generic drug product contained the same active ingredient as the reference listed drug.

d. FDA's decision to approve a generic cefuroxime axetil drug product whose cefuroxime axetil is in partially crystalline form is consistent with past generic drug product approvals

Generally a difference in the physical form of an active ingredient in a generic drug product from the physical form of the active ingredient in the reference listed drug, including a difference in the crystalline structure of the active ingredient, does not bar the approval of a proposed generic drug product.

FDA has approved numerous generic drug products in which the physical form of the active ingredient differs from the physical form of the active ingredient in the reference listed drug. Regarding different polymorphs, FDA has approved generic drugs whose active ingredients have a crystalline structure even though the active ingredient of the reference listed drug has an amorphous structure, and vice versa. For example, DuPont Pharma's Coumadin contains a crystalline form of warfarin sodium; one of the approved generic drug products contains warfarin sodium in the amorphous form. The *USP* monograph for Warfarin Sodium states that it is "an amorphous solid or a crystalline clathrate."³⁹ FDA also has approved generic drugs that contain the active ingredient in a different crystalline form from the crystalline form contained in the reference listed drug (e.g., famotidine, ranitidine).

In addition, the Agency has approved generic drugs in which the active ingredient differs from that in the reference listed drug with respect to solvation or hydration. For example, FDA has approved a terazosin hydrochloride anhydrous product as a generic version of Hytrin, Abbott Laboratories' terazosin hydrochloride dihydrate product; the USP has proposed a single drug substance monograph for Terazosin Hydrochloride.⁴⁰

FDA's scientific expertise and experience have shown that a difference in the physical form of the active ingredient in a generic drug product from the physical form of the active ingredient in the reference listed drug, including a difference in the crystalline structure of the active ingredient, does not prevent a finding of therapeutic equivalence.

³⁹ *USP 24* at 1750; *see also USP 25* at 1806-08.

⁴⁰ In-Process Revision, *Pharmacopeial Forum* 26(3), May-June 2000, at 747-52; *see also Pharmacopeial Forum* 27(2), Mar.-Apr. 2001, at 2202-07.

e. FDA's view that wholly or partially crystalline cefuroxime axetil is the "same" as amorphous cefuroxime axetil is not inconsistent with that of the international community

In a supplement to its citizen petition submitted on October 16, 2001, PDI states (Oct. 16 PDI Suppl. at 2) that the *Pharmacopoeia Europa (Ph Eur)*, *British Pharmacopoeia (BP)*, and *Chinese Pharmacopoeia* drug substance monographs for cefuroxime axetil require that the drug substance be in amorphous form and have a specified isomeric mixture. PDI maintains (*id.* at 3) that this requirement shows a lack of support in the international scientific community for the proposition that crystalline cefuroxime axetil may be considered the same as amorphous cefuroxime axetil. PDI also contends (*id.*) that approval of generic drugs containing both crystalline and amorphous cefuroxime axetil would be contrary to the goal of international regulatory harmonization under the ICH because approval would permit U.S. marketing of a drug product that likely would not be approved by other international regulatory authorities. PDI believes that such an approval would create disharmony and confusion in the global pharmaceutical market without any offsetting benefit for the American or international public (*id.* at 4).

PDI's comments about how the international community regards amorphous and crystalline cefuroxime axetil are misplaced. First, neither the *BP* nor the *Ph Eur* requires that cefuroxime axetil be in amorphous form. *BP* drug substance monographs include a section entitled "Characteristics" that describes certain physical characteristics of the drug substance; *Ph Eur* monographs that are incorporated into the *BP* have a corresponding section entitled "Characters." The *BP* drug substance monograph for cefuroxime axetil incorporates the *Ph Eur* monograph, so it has a "Characters" section.⁴¹ According to the General Notices of the *BP*, "[s]tatements given under the sideheading Characteristics are not to be interpreted in a strict sense and are not to be regarded as requirements."⁴² Because the reference to the amorphous form of cefuroxime axetil appears in the Characteristics (Characters) section of the *BP/Ph Eur* monograph, the amorphous form is not a requirement of either monograph, contrary to PDI's claim. Second, like the *USP* cefuroxime axetil monographs, the *BP* and *Ph Eur* monographs primarily reflect information submitted by GSK. FDA is confident that once international regulatory bodies have been presented with the data that have recently been made available to FDA and the *USP*, any current "disharmony" in the international community regarding cefuroxime axetil will be resolved (in favor of a decision that different polymorphs may be permitted under the same monograph).⁴³

⁴¹ *British Pharmacopoeia 2001 (BP 2001)*, Vol. I, at 349.

⁴² *Id.* at 10.

⁴³ For example, statements in a supplementary section of the *BP* strongly suggest that British officials would respond in a like fashion. The section on "Polymorphism" in *BP 1998* states:

For most pharmaceutical and medicinal substances it will not usually be appropriate or necessary for the monograph to control the morphic form. . . . In future the British Pharmacopoeia will include a specific statement that the material exhibits polymorphism, where it is known that this readily occurs under normal laboratory and manufacturing conditions. In the rare cases where it is

f. FDA currently expects an ANDA applicant to demonstrate that its proposed cefuroxime axetil product has a diastereoisomer ratio falling within a certain range

PDI maintains (PDI Petition at 19) that, to be eligible for approval, in addition to the same crystalline structure, the active ingredient in a generic cefuroxime axetil drug product must have the same stereoisomeric mixture as the active ingredient in the reference listed drug. PDI states that Ceftin contains amorphous cefuroxime axetil with a fixed-ratio mixture of R- and S-isomers. PDI contends (*id.* at 20) that changes to both the crystalline structure and stereoisomeric mixture of cefuroxime axetil will alter the solubility and bioavailability of the drug. Therefore, PDI argues (*id.*) that there is no justification to allow generic manufacturers to deviate from the standards of chemical identity of cefuroxime axetil that apply to Ceftin.

The *USP* monograph for cefuroxime axetil contains a specification for diastereoisomer ratio: the ratio of cefuroxime axetil diastereoisomer A to the sum of the cefuroxime axetil diastereoisomers A and B must be between 0.48 and 0.55.⁴⁴ FDA currently expects an applicant seeking approval of a generic version of Ceftin to demonstrate that its proposed cefuroxime axetil product meets this specification (among others).

g. FDA will not approve a proposed generic cefuroxime axetil drug product unless the manufacturer institutes whatever controls are necessary to ensure that the product meets the requirements of the Act and FDA regulations

GSK maintains (GSK Petition at 5) that even if the *USP* monograph did not specify the amorphous form, FDA should require the amorphous form, given the Agency's "previously stated policy and the significant product quality ramifications" that the petitioner discusses (GSK Petition at 7-11).

considered necessary, there will be a specific statement that the pharmacopoeial material is limited to one polymorph. *This approach will provide for amendment of the monograph if it becomes apparent that the material is unjustifiably restricted to one polymorph* (Vol. II, Suppl. Ch. I B, at A322 (emphasis added)).

In *BP 2001*, the "Polymorphism" section states:

Where the active ingredient is known to exist in more than one morphic form and the choice of polymorph is critical with regard to bioavailability and/or stability, the method of manufacture should ensure the presence of the correct amount of the desired polymorph in the preparation. In future the side heading 'Production' will be used to draw attention to control of morphic form during manufacture in cases where morphic form is known to be important (Vol. II, Suppl. Ch. I B, at A406).

Thus, it appears that the *BP* concurs with FDA and the *USP* in that concerns raised by differences in physical form should be addressed through manufacturing controls.

⁴⁴ *USP 24* at 355.

As explained above, FDA's general policy is that different polymorphs of a drug substance do not constitute different active ingredients. As discussed elsewhere in this response, FDA disagrees with GSK's conclusion that amorphous cefuroxime axetil has greater bioavailability than wholly or partially crystalline cefuroxime axetil, with significant effects on product performance. To be eligible for ANDA approval, a generic cefuroxime axetil drug product need not have an active ingredient in amorphous form. As in any ANDA review, FDA will not approve a proposed generic cefuroxime axetil drug product unless the manufacturer institutes whatever controls are necessary to ensure that the product meets the requirements of the Act and FDA regulations, including "sameness."

h. Ranbaxy's statements made in the course of patent litigation are not directly relevant to FDA's review of Ranbaxy's ANDA

PDI cites (PDI Petition at 13-14) statements by Ranbaxy in the patent infringement proceeding in support of PDI's argument that Ranbaxy's partially crystalline cefuroxime axetil drug product does not have the same active ingredient as Cefitin.

Statements that Ranbaxy has made in the patent infringement case suggesting that its drug product has a different active ingredient than Cefitin are not directly relevant to FDA's review of Ranbaxy's ANDA. The results of a patent infringement suit have no direct bearing on FDA's determination of the sameness of a proposed generic drug product under § 314.92(a)(1). The legal standards for determining "sameness" under federal patent law are different from those that apply under the Act and FDA regulations for determining "sameness" for purposes of generic drug approvals. In fact, in enacting the Drug Price Competition and Patent Term Restoration Act of 1984 (Waxman-Hatch Act), Public Law 98-417 (1984), which expanded the universe of drugs for which FDA would accept ANDAs, Congress contemplated that generic manufacturers would develop drugs that would not infringe on existing patent(s) on the reference listed drug (i.e., not be the "same" in some significant way for the purposes of patent law), yet still be eligible for approval under section 505(j) of the Act. Indeed, the Waxman-Hatch Act provides a specific mechanism for generic drug manufacturers to develop drugs without infringing patents, through the submission of a so-called paragraph IV certification under section 505(j)(2)(A)(vii)(IV) of the Act.⁴⁵ It is possible, therefore, that seemingly contradictory arguments might be made in a patent infringement case and in support of an ANDA.

⁴⁵ Under section 505(j)(2)(A)(vii) of the Act, an ANDA applicant must submit a certification with respect to each patent listed in the *Orange Book* that claims the listed drug or a use for the listed drug for which the applicant seeks approval and for which certain information is required to be filed. The ANDA applicant must certify (I) that such patent information has not been filed, (II) that such patent has expired, (III) the date on which such patent will expire, or (IV) that such patent is invalid or will not be infringed by the manufacture, use, or sale of the new drug for which the application is submitted. The ANDA applicant's assertion that the generic product for which it seeks approval as meeting the standards of section 505(j) of the Act will not infringe the innovator's patents may then be tested through patent infringement litigation.

2. A Cefuroxime Axetil Drug Product Containing Cefuroxime Axetil in Crystalline Form Would Have the Same Labeling as the Reference Listed Drug Except for Differences Permitted by Law

GSK notes (GSK Petition at 6) that the package insert for Ceftin describes the active ingredient as being "in the amorphous form." GSK contends that approving a drug product wholly or partially composed of the crystalline form of cefuroxime axetil would flout the requirement that the labeling of an ANDA product be the same as that of the reference listed drug. GSK contends that under 21 CFR 314.94(a)(8)(iv), the only permissible differences in labeling are differences in "expiration date, formulation, bioavailability, or pharmacokinetics, labeling revisions made to comply with current FDA labeling guidelines or other guidance, or omission of an indication or other aspect of labeling protected by patent or accorded exclusivity. . . ." GSK maintains that the issue of amorphous versus crystalline is a difference in active ingredient, not of formulation.

GSK's claims are misplaced. The Act requires the ANDA applicant to show that "the labeling proposed for the new [generic] drug is the same as the labeling approved for the listed drug. . . except for changes required because of differences approved under a petition filed under [505(j)(2)(C) of the Act] or because the new drug and the listed drug are produced or distributed by different manufacturers." *See* section 505(j)(2)(A)(v) of the Act; *see also* section 505(j)(4)(G) of the Act.⁴⁶

FDA regulations similarly require, under 21 CFR 314.94(a)(8)(iv), that the "[l]abeling . . . proposed for the [generic] drug product must be the same as the labeling approved for the reference listed drug, except for changes required because of differences approved under a petition filed under § 314.93 *or because the drug product and the reference listed drug are produced or distributed by different manufacturers*" (emphasis added).⁴⁷ Section 314.94(a)(8)(iv) then lists examples of permissible differences in labeling that may result because the generic drug product and reference listed drug product are produced or distributed by different manufacturers.

⁴⁶ The legislative history also makes clear that Congress never intended the "same labeling" provision to require identical labels for the generic drug product and the reference listed drug. The House report states, "The Committee recognizes that the proposed labeling for the generic drug may not be exactly the same. For example, the name and address of the manufacturers would vary as might the expiration date for the two products. Another example is that one color is used in the coating of the listed drug and another is used in that of the generic drug. The FDA might require the listed drug maker to specify the color in its label. The generic manufacturer, which has used a different color, would have to specify a different color in its label." *See* House Report on Drug Price Competition and Patent Term Restoration Act, H. Rep. No. 98-857, 98th Cong. 2d Sess. at 22 (1984), *reprinted in* 1984 *U.S.C.C.A.N.* 2647 at 2655.

⁴⁷ *See generally* *Zeneca, Inc. v. Shalala*, 1999 U.S. Dist. LEXIS 12327 (Aug. 11, 1991), *aff'd*, 213 F.3d 161 (4th Cir. 2000).

FDA interprets this codified language broadly, as reflected by the plain language of § 314.94(a)(8)(iv), which includes, among other things, differences in expiration date, formulation, bioavailability, and pharmacokinetics. The plain language of § 314.94(a)(8)(iv) explicitly recognizes that these differences listed in the regulation are examples; therefore, § 314.94(a)(8)(iv) recognizes that there are other differences in labeling between generic drug products and reference listed drugs that are permissible due to the fact that the generic drug product and reference listed drug product are produced or distributed by different manufacturers.

Consistent with this regulatory scheme, FDA may approve a generic cefuroxime axetil tablet product whose labeling states that the active ingredient is wholly or partially in crystalline form. The difference between crystalline and amorphous forms of cefuroxime axetil is one of physical form, rather than active ingredient. This difference in the physical form of cefuroxime axetil, as explained earlier, is a permissible difference under the Act for the purposes of generic drug approvals. That is, a difference in the physical form of an active ingredient in the generic drug product from the physical form of the active ingredient in the reference listed drug, including a difference in the crystalline structure of the active ingredient, does not bar the approval of a proposed generic drug product. An ANDA applicant (e.g., manufacturer) could produce and obtain approval of a generic drug product that contains a different physical form of cefuroxime axetil than the amorphous form of cefuroxime axetil in the reference listed drug, Ceftin; the labeling differences resulting from the fact that a generic drug product and the reference listed drug are produced or distributed by different manufacturers would be permissible. Consequently, FDA may approve a generic cefuroxime axetil tablet product whose labeling indicates that the active ingredient is wholly or partially in crystalline form.

Additionally, GSK's claim that § 314.94(a)(8)(iv) specifies *all* of the permissible labeling differences between generic and reference listed drug products is incorrect. As noted above, § 314.94(a)(8)(iv) provides, among other things, that "differences between the applicant's proposed labeling and labeling approved for the reference listed drug labeling [resulting from the fact that a generic drug product and the reference listed drug are produced or distributed by different manufacturers] *may include* differences in expiration date, formulation, . . ." etc. (emphasis added). The regulation does not state that these are the *only* acceptable differences between generic and reference listed drug labeling. Rather, the provision lists the differences as examples of acceptable differences in labeling resulting from the fact that a generic drug product and the reference listed drug are produced or distributed by different manufacturers.

GSK also contends (GSK Petition at 6) that a generic product whose active ingredient is wholly or partially in crystalline form would be unapprovable because the generic drug would have to be labeled with a different name than the listed drug, due to its failure to meet the current *USP* monograph. GSK notes that, under 21 CFR 299.5(a), "[t]he name by which a drug is designated shall be clearly distinguishing and differentiating from any name recognized in an official compendium unless such drug complies in identity with the identity prescribed in an official compendium under such recognized name." GSK argues that labeling a drug product containing crystalline cefuroxime axetil as "cefuroxime axetil" would constitute misbranding because the product would not comply with the standards for identity in the *USP*.

GSK made this argument after the proposed revision to the *USP* cefuroxime axetil monograph, but before the revision had been made final. This argument, as discussed earlier, is no longer an issue. As discussed above, the revised cefuroxime axetil monograph now includes both amorphous and crystalline forms of the drug substance. A cefuroxime axetil drug product whose active ingredient is wholly or partially in crystalline form would be labeled with the same name as a drug product whose active ingredient is amorphous.

PDI notes (PDI Petition at 21-22) that the *USP* monograph now requires the labeling for cefuroxime axetil drugs to specify which form of cefuroxime axetil comprises the active ingredient. PDI contends, therefore, that even the revised monograph does not permit a drug product containing any crystalline cefuroxime axetil to be labeled in the same manner as amorphous cefuroxime axetil.

That the *USP* cefuroxime axetil monographs now specify that a cefuroxime axetil drug substance or drug product is to be labeled to state the physical form of the active ingredient does not mean that the different physical forms are understood to be different active ingredients. The *USP* could have created separate monographs for the amorphous cefuroxime axetil drug substance and crystalline cefuroxime axetil drug substance (and done the same for cefuroxime axetil tablets).⁴⁸ Instead, the *USP* decided to include specifications regarding the physical form of the active ingredient in drug substance and drug product labeling. Moreover, as explained earlier, this difference in the physical form of cefuroxime axetil is a permissible difference under the Act for the purposes of generic drug approvals. The labeling differences resulting from the fact that a generic drug product and the reference listed drug are produced or distributed by different manufacturers are labeling differences permitted by law.

B. As With All ANDAs, FDA Will Require Appropriate Manufacturing Controls for the Approval of a Generic Cefuroxime Axetil Drug Product

GSK maintains (GSK Petition at 7) that having crystalline material in a cefuroxime axetil formulation raises the possibility that individual batches could differ significantly from each other due to the many forms (at least seven) of crystalline cefuroxime axetil. GSK states that there could be a myriad of combinations of the different forms, which could produce potential variability in product quality, efficacy, and clinical performance. Therefore, GSK contends that any formulation that includes crystalline material must be tightly controlled by establishing certain drug substance and drug product specifications.

As it does with any generic drug product, FDA will require appropriate controls on the manufacture of any proposed cefuroxime axetil drug product containing the active ingredient in wholly or partially crystalline form. In the process of reviewing ANDAs, the Agency assures that appropriate standards of product quality are met. Every ANDA applicant must establish specifications and methods to ensure the identity, strength, quality, and purity of its proposed

⁴⁸ Even the adoption of separate monographs would not necessarily have meant that the *USP* regarded these products as having different active ingredients. The *USP* has occasionally established different drug product monographs for different physical forms of the same active ingredient. Generally, however, the *USP*'s practice is to have a single monograph for drug products having the same active ingredient in different physical forms.

drug substance and drug product, as well as the bioavailability of the drug product, in accordance with section 505(j)(4) of the Act and 21 CFR 314.50(d)(1) (see also § 314.94(a)(9)(i)). Physical form is often one subject of specifications. Controls for component quality, the manufacturing process, and drug product characteristics are used to provide assurance that expectations of efficacy and clinical effectiveness are met. When there is concern that changes affecting product performance might develop, FDA seeks assurances that such changes are capable of being monitored and that product specifications will preclude changes detrimental to product performance. As with all generic drug products, FDA will require adequate controls for any generic drug product containing crystalline cefuroxime axetil to ensure that the drug product manufactured is the “same as” the reference listed drug.

GSK attaches to its petition (in Exhibit E) a Declaration of Dr. Stephen Byrn, Chairperson of FDA’s Pharmaceutical Science Advisory Committee (Byrn Declaration). GSK states (GSK Petition at 8) that Dr. Byrn conducted a study of various solid-state forms of cefuroxime axetil using Decision Tree #4 (Investigating the Need to Set Acceptance Criteria for Polymorphism in Drug Substances and Drug Products) of the *ICH Q6A* draft guidance. GSK contends that Dr. Byrn’s study supports GSK’s position that cefuroxime axetil drug products containing crystalline material in any amount would likely have quality characteristics that differ from those of Ceftin products. GSK states (GSK Petition at 9) that Dr. Byrn’s data show that the solubility of the various components of an amorphous-crystalline mixture could vary 65-fold. On the basis of Dr. Byrn’s data, GSK maintains that the differential solubilities of the crystalline isomers could cause in vivo dissolution and absorption to vary markedly from one batch to the next if there were underlying variation in the relative proportion of the crystalline isomers. Therefore, GSK claims that the need for robust analytical controls for release and stability testing is evident.

Dr. Byrn’s application of Decision Tree #4 of *ICH Q6A* to the issue of cefuroxime axetil crystallinity is flawed. He assumes that drug product performance testing cannot provide adequate control if there are changes in the polymorph ratio (e.g., as a result of dissolution) (see Decision Tree #4, Section 3 (62 FR 62890 at 62902)). Dr. Byrn posits, without providing any substantiation, that “performance testing, e.g., conventional dissolution testing, is not adequate to contend with the solubility profile displayed by cefuroxime axetil and the associated variability in bioavailability” (Byrn Declaration at 7-8). As discussed above, FDA will require any applicant seeking approval of a proposed generic cefuroxime axetil product to demonstrate that satisfactory standards of product quality are met. With respect to Ranbaxy’s ANDA, the Agency reviewed the information in the application. FDA concluded that the sponsor has established appropriate performance tests to ensure adequate controls to enable the product to meet the Act’s requirements and FDA regulations.

GSK states (GSK Petition at 9) that bioavailability differences between crystalline and amorphous forms of cefuroxime axetil anticipated by Dr. Byrn are confirmed by in vivo data, citing four studies that GSK included as attachments to its petition (GSK Petition at 9-10 and footnotes 9, 11-13). The four studies cited are of questionable relevance to determining the bioequivalence of a cefuroxime axetil drug product containing the active ingredient in wholly or partially crystalline form to the reference listed drug, Ceftin. Following are summaries of those studies and FDA’s assessment of their relevance.

- (1) **Study No. GMH/87/021, "To Compare the Serum Level Profile of Amorphous and Crystalline Cefuroxime Axetil; A Pilot Study With Dosing After Food" (1987).** Six healthy volunteers were studied to assess the relative bioequivalence of amorphous and crystalline cefuroxime axetil. Doses were equivalent to 250 mg of cefuroxime taken as aqueous suspensions after a standard breakfast. Serum levels of cefuroxime were measured. Mean values of AUC_{0-8} ⁴⁹ were comparable between the two treatments. For crystalline cefuroxime axetil, the mean C_{max} ⁵⁰ value was 11.8% lower than the mean C_{max} for amorphous cefuroxime axetil. This difference was not statistically significant.

FDA's assessment: The findings from this study do not support the claim that cefuroxime axetil from the crystalline material is less bioavailable than that from the amorphous material. The study showed that cefuroxime axetil bioavailability was comparable whether the crystalline form or amorphous form was administered as an oral suspension because the differences were not shown to be statistically significant.

- (2) **Study No. HVT/80/30, "Human Volunteer Trial to Investigate the Urinary Recovery of Cefuroxime After Single Oral Doses of 250 mg Cefuroxime as E47 Ester in Three Different Forms" (1980).** This six-way crossover study was designed to compare suspensions of micronized and unmiconized crystalline, microcrystalline, and amorphous forms of cefuroxime axetil, each containing isomers A and B in the ratio of 50:50. Each treatment was given under fasting conditions to 12 volunteers. The urinary recoveries (0-12 hours) of cefuroxime axetil averaged 42% (amorphous), 35% (microcrystalline), and 31% (crystalline), suggesting an average relative bioavailability of 75% for the crystalline form. The differences between amorphous and crystalline or microcrystalline forms were statistically significant. The difference between micronized and unmiconized material was not statistically significant. The study demonstrated that urinary recoveries were significantly lower after dosing with the crystalline form compared with the amorphous form.

FDA's assessment: The findings from Study No. GMH/87/021 showed that cefuroxime axetil bioavailability was comparable whether the crystalline form or amorphous form was administered as an oral suspension. Although the findings from Study No. HVT/80/30 do show some statistical significance, this may be due to the fact that there is a food effect on cefuroxime axetil bioavailability from the oral suspension. In Study No. HVT/80/30, subjects fasted, and cefuroxime axetil bioavailability from the crystalline form was significantly lower than from the amorphous. In Study No. GMH/87/021, subjects were fed, and there was no significant difference in cefuroxime axetil AUC and

⁴⁹ AUC means "area under the curve," which in this context refers to a measurement of the extent of absorption of a drug in the body as expressed in the resulting area under the plasma concentration-time curve (*Orange Book* at ix-x). The "0-8" subscript refers to calculation of the last measured concentration, i.e., after 8 hours (see id.).

⁵⁰ C_{max} means "maximum concentration," which in this context refers to the maximum or peak concentration of a drug in the body (*Orange Book* at x).

C_{max} , whether crystalline or amorphous material was given. Cefdin's labeling mentions the food effect and states that the suspension must be administered with food. Because cefuroxime axetil oral suspension must be given with food in clinical practice, Study No. HVT/80/30 (which used fasted subjects) does not support GSK's petition.

- (3) **Study No. UCP/89/028, "An Evaluation of the Bioequivalence of Cefuroxime Axetil Crystalline Isomers and Tablets in Healthy Adult Male Volunteers" (1989).** Twenty-four volunteers were studied to evaluate the bioequivalence of oral solutions of cefuroxime axetil crystalline isomers A, B, and a mixture of A and B compared with Cefdin (amorphous racemate) as a reference formulation. This was a four-way crossover study. Doses were equivalent to 250 mg of cefuroxime axetil as an aqueous solution for the crystalline isomer formulations or as a tablet for the amorphous racemate. Each dose was administered with a standardized breakfast. The serum pharmacokinetic parameters C_{max} and AUC_{0-inf} ,⁵¹ in addition to the percent of dose excreted in urine, were used to evaluate statistical differences between the test treatment groups. For the three test crystalline solution formulations, the mean C_{max} and AUC_{0-inf} values were lower than those for the reference tablet. Neither C_{max} nor AUC_{0-inf} for any cefuroxime isomer formulation compared with the tablet was within the 80-125% range.⁵² None of the urine parameters for any isomer formulation compared with the tablet were within the 80-125% range. Based on the statistical analysis of the serum and urine data, none of the three test 250-mg dose crystalline formulations administered as solutions was bioequivalent to a 250-mg dose of cefuroxime axetil tablet.

FDA's assessment: Study No. UCP/89/028 is not relevant to GSK's petition because the study compared two different dosage forms, an oral solution and a tablet. Bioavailability differences are often observed when two different dosage forms are administered. In addition, the study did not directly compare crystalline cefuroxime axetil with amorphous cefuroxime axetil, since, in this study, the crystalline cefuroxime axetil was dissolved in solution before dosing. In solution, cefuroxime axetil exists as free solvated molecules rather than within a crystalline lattice structure, as occurs in the solid phase. Because this study compared the bioavailability of a cefuroxime axetil oral solution with amorphous cefuroxime axetil in tablets, it is not relevant to the type of study required in an ANDA to demonstrate bioequivalence.

⁵¹ AUC_{0-inf} means the area under the curve extrapolated to infinity (*Orange Book* at x).

⁵² As discussed in the *Orange Book* (at x), the 80-125% range reflects use of the two one-sided test procedure for analyzing bioequivalence studies. The first test determines whether a test product substituted for a reference listed product is significantly less bioavailable. The second test determines whether a reference listed product substituted for a test product is significantly less bioavailable. A difference of greater than 20% for each of the tests is deemed significant. This is expressed as a limit of test average/reference average of 80% for the first test and a limit of reference average/test average of 80% for the second test. By convention, all data are expressed as a ratio of the average response (AUC and C_{max}) for generic/reference, so the limit expressed in the second test is 125% (reciprocal of 80%).

- (4) **Study No. GPK/91/003, "A Study to Assess the Relative Bioavailability of Cefuroxime From an Oral Aqueous Suspension of Crystalline Cefuroxime Axetil in Comparison with an Amorphous Tablet in the Fed and Fasted State" (1991).** In this four-way crossover study, 24 volunteers were studied to compare the serum concentrations and urinary recoveries of cefuroxime from single 250-mg oral doses of cefuroxime axetil given both as an aqueous suspension of crystalline cefuroxime axetil and as an "RS3" tablet in both the fed and fasted states. Under fasted conditions, for the test crystalline suspension, the mean C_{max} and AUC_{0-12} values were lower than those for the reference tablet, and the 90% confidence intervals were within the 80-125% range for C_{max} , AUC_{0-12} , and 12-hour urinary data. Under fed conditions, for the suspension of crystalline cefuroxime axetil, the mean C_{max} value was 32% lower than that for the tablet, and only AUC_{0-12} was within the 80-125% range for the tablet. In terms of the AUC data, the two formulations were considered bioequivalent in the fed and fasted states. In terms of C_{max} , the two formulations were considered bioequivalent only under fasted conditions.

FDA's assessment: Because Study No. GPK/91/003 compared an oral suspension of crystalline cefuroxime axetil with a tablet containing amorphous cefuroxime axetil, it is not relevant to a demonstration of bioequivalence for ANDA purposes. It is not possible to determine whether the differences in bioavailability were due to differences in morphic form or differences in dosage form. As stated above, bioavailability differences are often observed when two different dosage forms are administered. The differences in dosage form may have contributed significantly to the study outcome. The labeling for Ceftin clearly states that the oral suspension is not bioequivalent to the tablet.

On October 30, 2000, GSK submitted two additional studies in support of its petition:

- (1) **Study No. HVT/77/14, "Human Volunteer Trial to Investigate the Oral Absorption of Isomers A and B of Cefuroxime E47 Ester" (1977).** In this study, six volunteers took oral suspension doses of 250-mg cefuroxime axetil as the E47 (axetil) ester. Five took isomer A (crystalline isomer), five took isomer B (crystalline isomer), and two took a mixture of both. Average 24-hour urinary recoveries were 21% for isomer A, 37% for isomer B, and 32% for the 50:50 mixture. The average observed peak serum cefuroxime axetil concentration was 2.2 ug/mL after taking isomer A and 3.3 ug/mL after taking isomer B. The average peak serum level for the two volunteers who took A + B was 1.7 ug/mL. All these peaks occurred between 1 and 3 hours after dosing. One volunteer (#5) experienced mild diarrhea after isomer B. One volunteer (#3) who took isomer A complained of severe abdominal cramping pains starting 3 days after the trial. The sponsor concluded that isomer B was better absorbed than isomer A and that the absorption of isomer B was not better than that of the mixture of the isomers used in previous human volunteer experiments. The sponsor speculated that the severity of the gastrointestinal upset in volunteer #3 may be attributed to the fact that cefuroxime axetil is unsuitable for oral administration unless it is completely absorbed.

FDA's assessment: Although Study No. HVT/77/14 did not directly compare the crystalline and amorphous forms of cefuroxime axetil, it appears that GSK submitted this study to support an argument that incomplete absorption of the crystalline form is associated with toxicity. GSK did not, however, provide convincing evidence to support this statement. GSK suggests that volunteer #3's gastrointestinal adverse event was attributable to the incomplete absorption of crystalline cefuroxime axetil. However, pharmacokinetic data showed that cefuroxime axetil systemic exposure in this subject was actually greater than the mean exposure of the other subjects.

- (2) **Study No. HVT/80/27, "Human Volunteer Trial to Investigate the Urinary Recovery of Cefuroxime After Single Doses of 250 mg Cefuroxime as E47 Ester in Four Different Isomer Ratios" (1980).** Ratios of A:B (crystalline isomers) of 60:40, 50:50, 40:60, and 30:70 were given in aqueous suspension at doses of 250-mg cefuroxime axetil as the axetil ester to 12 volunteers in a double-blind, crossover study on successive days. The respective 12-hour urinary recoveries of cefuroxime averaged 35.8%, 40.6%, 39.6%, and 41.5%. Two-way analysis of variance showed that there were no significant differences between treatments.

FDA's assessment: Study No. HVT/80/27 is not relevant to GSK's petition because it only compared the bioavailability of various mixtures of crystalline cefuroxime axetil isomers A and B. The study did not include treatment with the amorphous form of cefuroxime axetil.

In summary, the bioavailability/bioequivalence studies that GSK submitted do not support its contention that crystalline cefuroxime axetil exhibits inferior bioavailability compared with amorphous cefuroxime axetil. Moreover, findings from a bioequivalence study that GSK submitted in support of its own NDA for Cefin tablets conflict with GSK's position that the high aqueous solubility of the amorphous form of cefuroxime axetil results in superior bioavailability. The study showed that a batch of amorphous cefuroxime axetil with a rapid dissolution rate was bioequivalent to a batch of amorphous cefuroxime axetil with a slow dissolution rate. Thus, marked differences in solubility between the two batches had no effect on bioequivalence.

PDI maintains (PDI Petition at 17) that "there is no basis in sound science . . . 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." PDI further states (id.) that "[a]pproval of the pending ANDAs [submitted by Ranbaxy and any other applicant] 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 decisionmaking in the interest of economic expediency and ignore the clear statutory mandate requiring 'sameness.'"

FDA disagrees with PDI's conclusions about the relevant science in this matter. As stated above, FDA is obligated to follow the Act and FDA regulations in determining whether it may approve a proposed generic drug product. If the generic applicant provides sufficient data and other information on manufacturing, conditions of use, active ingredient(s), bioequivalence,

labeling, and other matters necessary for approval under section 505(j)(4) of the Act, FDA must approve the application. The existence of published literature that may reach a different conclusion about whether wholly or partially crystalline forms of cefuroxime axetil are bioequivalent to the amorphous form contributes to FDA's general knowledge of cefuroxime axetil drug products, so this information is useful in assessing the data in ANDAs. The Agency's review of a specific ANDA for a proposed generic cefuroxime axetil drug product is based on the evidence submitted by the applicant, as assessed using FDA's expertise and experience. FDA carefully reviewed the information in Ranbaxy's ANDA. The Agency concluded that Ranbaxy met the requirements for approval, including demonstrating that its cefuroxime axetil drug product is bioequivalent to GSK's Ceftin. Moreover, FDA will not, "in the interest of economic expediency" or for any other reason, abandon the scientific principles that guide its decisionmaking on ANDAs. FDA is acutely aware that it cannot maintain the public's confidence in the safety and effectiveness of generic drugs if the Agency does not base its decisions on sound science.

GSK maintains (GSK Petition at 11) that even if FDA were inclined to permit the use of crystalline cefuroxime axetil in generic cefuroxime axetil products, consistent and reliable product performance would require stringent acceptance criteria to ensure that there was no batch-to-batch or stability-related variation in (1) the ratio of crystalline to amorphous drug, (2) the ratio of diastereoisomers, and (3) the ratio of polymorphs. GSK contends that for both the drug product and the drug substance, standard performance testing alone is inadequate, so there must be quantitative analytical controls.

As stated above, evaluation of the adequacy of controls is part of FDA's normal ANDA review process. The Agency makes determinations regarding the need for such controls based on the specific product, relying on information available through referenced drug master files and in the submitted application. It is these application-based data that are used to evaluate the adequacy of controls to ensure acceptable parameters for a proposed drug product. FDA acknowledges that the processing of either the drug substance or the drug product might affect the characteristics of the drug product. The Agency takes these issues into consideration during the review process. Regardless of the controls that GSK uses for its Ceftin products, FDA will require appropriate controls as a condition of approval for any proposed generic product containing crystalline cefuroxime axetil. These controls may be different from and/or additional to the controls for Ceftin products. With respect to Ranbaxy's cefuroxime axetil product, the applicant demonstrated that it had established appropriate performance tests to ensure adequate control of its product.

IV. RESPONSE TO JUNE 4, 2001, SUPPLEMENT TO GSK PETITION

In the June 4, 2001, supplement to its petition, GSK repeats its contention that standard product performance testing alone (e.g., dissolution testing) is inadequate to control for potential variations in the solid-state form of cefuroxime axetil in formulations that include some proportion of crystalline drug substance (June 4 GSK Suppl. at 3). But GSK states that to the extent that dissolution testing does have a role in helping to monitor and regulate the quality of cefuroxime axetil tablets, such testing must not be compromised. Without citing any specific

data, GSK speculates that a generic manufacturer's proposed version of cefuroxime axetil may have had a dissolution profile outside of the tolerances of the current *USP* test, causing the manufacturer to seek approval of a less stringent alternative test. GSK contends (id. at 3-4) that the higher paddle speed and elimination of the 15-minute time point in the proposed revision of the *USP* Cefuroxime Axetil Tablets monograph would conflict with FDA's guidance on *Dissolution Testing of Immediate Release Solid Oral Dosage Forms* (August 1997).⁵³ GSK argues that these proposed changes reinforce its concern that a generic product containing crystalline cefuroxime axetil may not produce consistently acceptable in vivo product performance.

The guidance document references to paddle speed and time point that GSK cites apply to developing dissolution methods for new chemical entities.⁵⁴ The guidance document (at 3) notes:

In the case of a generic drug product, the dissolution specifications are generally the same as the reference listed drug. The specifications are confirmed by testing the dissolution performance of the generic drug product from an acceptable bioequivalence study. If the dissolution of the generic product is substantially different compared to that of the reference listed drug and the in vivo data remain acceptable, a different dissolution specification for the generic drug product may be set.

In approving any generic cefuroxime axetil drug product, FDA ensures that the ANDA applicant establishes the appropriate dissolution specifications for the product.

V. RESPONSE TO SEPTEMBER 10, 2001, SUPPLEMENT TO GSK PETITION

In the September 10, 2001, supplement to its petition, GSK contends that the USP's decision to revise the cefuroxime axetil and cefuroxime axetil tablets monographs effectively endorsed the proposition that amorphous cefuroxime axetil and crystalline cefuroxime axetil are materially different. GSK maintains (Sept. 10 GSK Suppl. at 2) that the USP recognized that amorphous

⁵³ The proposed monograph revision would increase the paddle speed from 55 rpm to 100 rpm. GSK notes that the guidance (at A-2) states, "In general, mild agitation conditions should be maintained during dissolution testing to allow maximum discriminating power and to detect products with poor in vivo performance. . . . [T]he common agitation (or stirring speed) . . . with the paddle method . . . is 50-75 rpm." Regarding the proposed elimination of the 15-minute time point, GSK notes that the guidance (at 6) states, "For poorly water soluble drug products . . . , dissolution testing at more than one time point for routine quality control is recommended to ensure in vivo product performance." FDA notes that the "Policies and Announcements" section of *Pharmacopeial Forum* 27(6), at 3226, announces changes with respect to the dissolution section.

⁵⁴ Those citations are from section IV.A of the guidance (at 4-5), entitled "Approaches for Setting Dissolution Specifications for a New Chemical Entity." Section IV.B of the guidance, entitled "Approaches for Setting Dissolution Specifications for Generic Products," states (at 5) that all approved drug products should meet *USP* dissolution test requirements if a compendial method exists. It further states (id.) that the Center for Drug Evaluation and Research's (CDER) Division of Bioequivalence may ask a generic drug manufacturer to submit additional dissolution data when scientifically justified.

cefuroxime axetil and crystalline cefuroxime axetil are sufficiently different so that the drug substance must be labeled as either amorphous or crystalline. GSK claims that if the two types of cefuroxime axetil were the same, there would be no reason to distinguish between them. GSK contends (*id.* at 3) that this is further evidenced by the USP's decision to amend the cefuroxime axetil tablets monograph to require that labeling indicate whether the tablets contain amorphous or crystalline cefuroxime axetil.

GSK's characterization of the USP's decisions regarding cefuroxime axetil is inaccurate. The fact that the USP modified the cefuroxime axetil monograph to allow for the inclusion of a crystalline form of cefuroxime axetil demonstrates that the USP regards crystalline and amorphous cefuroxime axetil as the same drug substance. FDA agrees that the *USP* instruction to label the cefuroxime axetil drug substance and drug product (tablets) as either amorphous or crystalline is to indicate the difference in physical form, not a difference in active ingredient. The USP often specifies this type of labeling instruction to reflect differences in the physical form of a particular drug substance or product.

GSK notes (Sept. 10 GSK Suppl. at 3) that the Acting Director of CDER's Office of Generic Drugs (OGD) stated in a memorandum to the USP that "differences in physical form are not relevant to a determination of a same active ingredient."⁵⁵ GSK maintains that this statement conflicts with the statement in the preamble to the 1992 final rule on ANDA regulations that, in some cases, FDA may prescribe additional standards that are material to the sameness of an active ingredient, beyond the standards of identity described in the *USP*.⁵⁶ GSK contends that the preamble statement constitutes an advisory opinion under 21 CFR 10.85(d)(1), and that under § 10.85(e), the statement represents the formal opinion of FDA and obligates the Agency to follow it until it is amended or revoked.

There is no conflict between the OGD Acting Director's statement and the 1992 preamble statement. The OGD Acting Director merely stated the general principle, as expressed in that preamble and in the *Orange Book*, that the physical form of a drug substance is not relevant to a determination of whether a generic drug product has the same active ingredient as the reference listed drug for the purposes of generic drug approvals. Although the 1992 preamble does allow for the possibility that FDA might, in some cases, require additional standards for crystalline structure, it states that in most cases, the *USP* standards will be sufficient — a principle that is affirmed by the *Orange Book* statement on the pharmaceutical equivalence of different polymorphs.

GSK contends (Sept. 10 GSK Suppl. at 4) that the preamble statement about additional standards gives FDA more latitude than the Act permits. GSK believes that an Agency position that it could ignore differences between crystalline and amorphous active ingredients where those differences affect the function of the ingredients would be arbitrary and capricious.

⁵⁵ Memorandum from Gary J. Buehler, Acting Director, Office of Generic Drugs, to the Executive Committee of the Council of Experts, USP, July 10, 2001.

⁵⁶ 57 Fed. Reg. 17950 at 17959.

GSK mischaracterizes the preamble statement about prescribing additional identity standards. The statement says that “in some cases, FDA may prescribe additional standards that are material to the ingredient’s sameness.”⁵⁷ This does not suggest that the Agency may simply ignore differences in the physical form of an active ingredient. Rather, the statement gives notice that FDA might, under certain circumstances, impose standards for identity beyond those specified by the *USP*. Specifically, if FDA were to conclude, based on available evidence, that an additional standard were material to the sameness of an active ingredient, it would require that a proposed generic drug product meet this standard before it could be regarded as having the same active ingredient as the reference listed drug in accordance with section 505(j)(4)(C) of the Act and § 314.92(a)(1). Thus, the statement on additional identity standards is fully consistent with FDA’s statutory obligation to make an independent (case-by-case) determination regarding the sameness of the active ingredient in a proposed generic drug product.

GSK contends that it is not rational for FDA to deem different salts and esters to *never* be the “same” active ingredient yet deem different crystalline and amorphous forms of a particular salt or ester to *always* be the same active ingredient. Under § 314.93(d)(3), a person must file a “suitability petition” for permission to submit an ANDA for a drug product that is not identical to a listed drug. This provision states that the petitioner must include, if the proposed drug product is a combination product with one different active ingredient (including a different ester or salt), information to show that the different active ingredient has been previously approved in a listed drug or is a drug that does not meet the definition of “new drug” in section 201(b) of the Act (21 U.S.C. 321(b)). GSK states (Sept. 10 GSK Suppl. at 4) that this means that a different ester or salt is always a different active ingredient, even if it could be shown that a tablet containing one salt form of a drug would be bioequivalent to a tablet containing a different salt form (or an ester form). GSK contends that it is not rational to deem different salts and esters to *never* be the “same” active ingredient yet deem different crystalline and amorphous forms of a particular salt or ester to *always* be the same active ingredient.

Different salts and esters of the same therapeutic moiety are regarded as different active ingredients because they have different chemical structures and, quite often, different adverse event profiles.⁵⁸ FDA has long regarded chemical structure as being fundamental to the identity of an active ingredient. Consequently, FDA regards different salts and esters of the same therapeutic moiety as pharmaceutical alternatives rather than pharmaceutical equivalents.⁵⁹ On the other hand, different polymorphs of an active ingredient have the same primary chemical structure (the differences are in physical form) and are considered pharmaceutical equivalents,⁶⁰

⁵⁷ 57 Fed. Reg. 17950 at 17959.

⁵⁸ For example, penicillin G sodium is medically necessary for renally impaired patients for whom excess potassium could predispose them to life-threatening arrhythmias and possible death. On the other hand, penicillin G potassium is medically necessary for cardiac patients for whom excess sodium could lead to similar serious adverse events.

⁵⁹ *Orange Book* at xvi.

⁶⁰ *Id.*

which means (among other things) that they are the same active ingredient(s).⁶¹ Differences in physical form alone do not prevent a finding of pharmaceutical equivalency with respect to the resultant drug products. In short, for the purposes of generic drug approvals, it is appropriate for FDA to treat salt/ester variations differently from variations in crystallinity because differences in chemical structure are more fundamental than physical form variations.

GSK cites (Sept. 10 GSK Suppl. at 4-5) *Serono Laboratories, Inc. v. Shalala*, 158 F.3d 1313 (D.C. Cir. 1998), to support its contention that a "concept of identity to the extent possible logically applies as well to identity in solid-state form, given the potentially different properties of different physical forms."

Serono provides support for the approval of a generic drug product containing a different physical form of the active ingredient than the physical form of the active ingredient in the reference listed drug. *Serono* involved a legal challenge to FDA's decision to approve an ANDA for a generic version of a menotropins product used to treat infertility. FDA maintained that an isoform variation in the active ingredient of the generic product did not preclude a "sameness" finding for purposes of ANDA approval under § 314.92(a)(1). The U.S. Court of Appeals for the District of Columbia Circuit agreed with FDA.

The Court of Appeals stated that the Act "does not unambiguously require the term 'same as' to be defined as complete chemical identity." *Serono*, 158 F.3d at 1320. The Court of Appeals upheld as reasonable the Agency's interpretation of the "sameness" statutory requirement, as well as the Agency's interpretation of the word "identical" in § 314.92(a)(1) (*id.* at 1321). Moreover, *Serono* acknowledged the appropriateness of a flexible "sameness" standard, noting that the Agency specifically rejected a proposal that would have required ANDA applicants to demonstrate that their active ingredients had the same physical and chemical characteristics, that their products contained no additional residues or impurities, "and that the stereochemistry characteristics and solid state forms of the drug have not been altered" (*id.* at 1321 n. 3 (quoting 57 Fed. Reg. 17950 at 17958-59)). The Court of Appeals recognized that the Agency adopted a "more flexible approach," whereby the Agency would consider an active ingredient in a generic drug product to be the "same" as that of the reference listed drug if it were to meet the same standards for identity (*id.*). The Court of Appeals noted the Agency's view that, in most cases, those standards for identity are described in the *USP*, but the Agency may prescribe additional standards when needed (*id.* (citing 57 Fed. Reg. 17950 at 17959)).

As for amorphous and crystalline forms of cefuroxime axetil, the Agency has carefully reviewed the relevant data available and concluded that an identical physical form is not essential to establishing the sameness of the active ingredient. FDA has determined that no additional standards, including standards on crystalline structure or stereoisomeric mixture, are necessary with respect to establishing the sameness of cefuroxime axetil in a generic cefuroxime axetil drug product. Different physical forms of cefuroxime axetil have the same primary chemical structure; they also have the same chemical identity. As discussed above, this determination is

⁶¹ *Id.* at vii.

consistent with FDA's standard approach to proposed generic drug products containing an active ingredient that has a different physical form from that contained in the reference listed drug.

GSK states (Sept. 10 GSK Suppl. at 5) that an ANDA containing both amorphous cefuroxime axetil and crystalline cefuroxime axetil is simply a combination product, combining two different active ingredients, as disclosed by its labeling in accordance with the revision of the *USP* monograph for Cefuroxime Axetil Tablets.

As discussed above, amorphous cefuroxime axetil and crystalline cefuroxime axetil are two different physical forms of the same active ingredient, not two different active ingredients. Consequently, a mixture of amorphous and crystalline forms of cefuroxime axetil does not result in a combination drug product; rather, the drug product would simply contain a different physical form of cefuroxime axetil than a drug product that contains only amorphous cefuroxime axetil or only crystalline cefuroxime axetil as the active ingredient. The *USP* specification to indicate the crystalline or amorphous form of cefuroxime axetil in the drug product labeling does not suggest that these physical forms constitute different active ingredients within a combination drug product. In fact, exactly the opposite is implied in the *USP*'s revision of the drug substance monograph to delete the reference to "amorphous" and thereby include different physical forms of cefuroxime axetil.

VI. PDI PETITION

PDI makes two requests not included in the GSK Petition. These are: (1) that FDA stay the approval of any pending ANDA for a generic drug containing a mixture of amorphous and crystalline cefuroxime axetil until either 30 months from the date on which GSK commenced a patent infringement action against that applicant, or the date on which a court enters a final judgment or order declaring GSK's '181 patent to be invalid and/or not infringed by that applicant's ANDA; and (2) that the Agency initiate a rulemaking proceeding pursuant to 5 U.S.C. § 553 to establish standards for consideration of ANDAs that seek approval of drug products that contain a different crystalline form and/or different stereoisomeric mixture of an active ingredient from that contained in a reference listed drug. For the reasons discussed below, FDA denies both of these requests.

A. A Thirty-Month Stay of Approval of ANDAs for Generic Cefuroxime Axetil Products Is Not Required by the Act and Is Not Appropriate

PDI requests (PDI Petition at 27) that FDA stay the approval of any pending ANDA for a generic drug containing a mixture of amorphous and crystalline cefuroxime axetil until either (1) 30 months from the date on which GSK commenced a patent infringement action against the applicant, or (2) the date on which a court enters a final judgment or order declaring GSK's '181 patent to be invalid and/or not infringed upon.

Section 505(j)(5)(B) of the Act imposes a 30-month stay of approval of a generic drug 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 regarding one of the patent

holder's patents. PDI notes (PDI Petition at 7) that because Ceftin is an antibiotic that was approved under section 507 of the Act (repealed by section 125 of FDAMA), its corresponding patents are not listed in the *Orange Book*. Consequently, any ANDA applicant seeking approval of a generic version of cefuroxime axetil has not been required to include in its application a certification, in accordance with section 505(j)(2)(A)(vii) of the Act, with respect to GSK's '181 patent.

PDI maintains (PDI Petition at 26) that the fact that GSK's '181 patent on cefuroxime axetil is not required to be listed in the *Orange Book* does not render that patent any less deserving of statutory protection than listed patents and does not alter the public policy concerns supporting the imposition of a stay. In support of its argument, PDI states that FDAMA did not include section 505(j)(5)(B) of the Act among those new drug provisions that will *not* apply to future ANDAs for which the reference listed drug at issue was an antibiotic drug that was approved under the now-repealed section 507. PDI maintains that if Congress had intended to keep the 30-month stay requirement in section 505(j)(5)(B) from applying to ANDAs for generic versions of antibiotics that had been approved under section 507, it could have mandated as much by including section 505(j)(5)(B) in the list of statutory provisions that would not apply to such drugs.

It is inappropriate to stay the approval of any generic version of cefuroxime axetil until the resolution of the patent infringement proceedings involving GSK's '181 patent. The Act does not even suggest, much less require, such a stay. As PDI notes, GSK's '181 patent was not required to be listed in the *Orange Book* because cefuroxime axetil is an antibiotic drug that was approved under section 507 of the Act. The patent listing provisions of the Act did not apply to antibiotics approved under section 507. Because GSK was not required to list its cefuroxime axetil patent in the *Orange Book*, ANDA applicants (including Ranbaxy and Apotex) seeking approval of a generic version of cefuroxime axetil are not required to make any certification with respect to the '181 patent under section 505(j)(2)(A)(vii) of the Act. Absent such certification, FDA cannot impose a 30-month stay of approval of any proposed generic version of Ceftin even though GSK has initiated a patent infringement action against the ANDA applicant.

Moreover, Congress did not intend to apply the 30-month stay provision to ANDAs for generic versions of antibiotics that the Agency had approved under section 507. In fact, Congress intended that all of the provisions of the Act related to marketing exclusivity and patent certification, including the 30-month stay requirement, would *not* apply to such ANDAs.⁶²

⁶² The House Report on H.R. 1411, the 1997 House bill on FDA regulatory modernization, states the following with respect to antibiotics:

The repeal of section 507 also results in applications for new antibiotic products being submitted to the FDA under all the requirements and benefits of section 505, including the granting of market exclusivity to all new drugs under the so-called Waxman-Hatch provisions. The Committee intends that the market exclusivity be limited to products that achieve the policy objective of increasing research toward the development of new antibiotics. Thus, the granting of market exclusivity to new antibiotic drugs is limited to those products that are New Chemical Entities and to products for which a New Drug Application has not been submitted prior to the date of enactment.

Section 125(d)(2)(A)-(B) of FDAMA lists the subsections of section 505 of the Act that will not apply to these ANDAs. All of the subsections of section 505 listed therein deal with patent issues, with two exceptions — (j)(4)(B) and (j)(4)(D). Before the enactment of FDAMA, subsections (j)(4)(B) and (j)(4)(D) dealt with patent certification and marketing exclusivity matters, which did not apply to antibiotics. However, as a result of FDAMA, *former* subsections (j)(4)(B) and (j)(4)(D) of section 505 have been recodified as subsections (j)(5)(B) and (j)(5)(D), and *current* subsections (j)(4)(B) and (j)(4)(D) now list two of the bases for denying approval of an ANDA (regarding previous approval of the proposed condition of use for the reference listed drug and the sameness of the proposed generic drug to the reference listed drug).⁶³ Congress clearly did not intend to exempt ANDAs for antibiotics from these fundamental provisions. Rather, Congress intended that the patent provisions that had formerly appeared as section 505(j)(4)(B) and (j)(4)(D) — including the 30-month stay requirement — would not apply to ANDAs for generic versions of antibiotics that had been approved under section 507.⁶⁴

House Rep. No. 105-310, 105th Cong., 1st Sess. 77 (1997).

⁶³ Under current section 505(j)(4)(B) of the Act, FDA may not approve an ANDA if the information submitted with the application is insufficient to show that each of the proposed conditions of use have been previously approved for the listed drug referred to in the application. Under current section 505(j)(4)(D)(i) of the Act, if an ANDA is for a drug whose route of administration, dosage form, or strength is the same as the route of administration, dosage form or strength of the listed drug referred to in the application, FDA may not approve the application if the information submitted in the application is insufficient to show that the route of administration, dosage form, or strength is the same as that of the listed drug. Under current section 505(j)(4)(D)(ii) of the Act, if the ANDA is for a drug whose route of administration, dosage form, or strength is different from that of the listed drug referred to in the application, FDA may not approve the application if no petition to file an application for the drug was approved under section 505(j)(2)(C) of the Act.

⁶⁴ FDA recognized Congress's intent to exempt antibiotics approved under section 507 of the Act from the 30-month stay provision in its proposed rule on "Marketing Exclusivity and Patent Provisions for Certain Antibiotic Drugs," 65 Fed. Reg. 3623 (January 24, 2000). In accordance with FDAMA, FDA issued this proposed rule to exempt marketing applications for certain antibiotic drug products from regulatory provisions governing marketing exclusivity and patents. The proposed rule states:

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).

Id. at 3623-24 (footnote omitted). The proposed rule further states that one of the provisions of section 505 of the Act that do not apply to applications for "prerepeal" antibiotic drugs is "[s]ection 505(j)(5)(B) (*providing for delayed effective dates of approval of ANDA's under patent provisions of the act*)" (id. at 3624) (emphasis added). In a footnote, FDA explains that FDAMA "added a new section 505(j)(3) of 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 n.2).

B. The Act and FDA's Existing Regulations and Guidance Are Sufficient for Making Determinations on ANDAs for Drug Products Whose Active Ingredients Have Different Physical Forms Than Those of Reference Listed Drugs

PDI states (PDI Petition at 27-28) that FDA should initiate a rulemaking proceeding pursuant to 5 U.S.C. § 553 to establish rules of general applicability, general policies, and interpretations of general applicability concerning the use of the ANDA procedure to obtain approval of proposed new drugs that differ in form (especially crystalline form) from a reference listed drug. PDI contends (*id.* at 28) that there are no specific rules or guidelines to direct FDA's review of ANDAs for such drugs or to guide the public and industry in these matters. PDI also states that FDA should suspend consideration of all ANDAs seeking approval of drugs that differ in form (especially crystalline form) from a listed drug and initiate a rulemaking proceeding. Thus, PDI appears to request that the Agency not approve any ANDAs for these types of drug until new rules are adopted.

FDA believes that the Act, existing regulations, preamble statements, and statements in the *Orange Book* provide an adequate basis to guide the Agency's decisionmaking on ANDAs seeking approval of a drug product whose active ingredient is in a different physical form than the active ingredient of the reference listed drug. As stated above, the Act gives FDA discretion with respect to the information that the Agency may consider in making a determination on the "sameness" of a proposed generic drug product. FDA regulations state that, to be the "same as" a reference listed drug, a proposed generic drug product must be, among other things, "identical in active ingredient(s) . . ." (§ 314.92(a)(1)). Statements in the preamble to the 1992 final rule on ANDAs and in the *Orange Book* make clear that, in most cases, a generic drug product whose active ingredient is a different polymorph of the active ingredient in a reference listed drug has the "same" active ingredient, in accordance with § 314.92(a)(1). The Agency does not believe that additional regulations on this subject are necessary at this time. Furthermore, even if FDA were to initiate a rulemaking proceeding, the Act and FDA regulations would not permit the Agency to suspend consideration of pending and future ANDAs of this type during the rulemaking.

Moreover, section 505(j) of the Act contains no language stating that regulations must be issued before FDA can make determinations with respect to the "sameness" of the active ingredient and the drug product. Congress may provide that Agency action may be undertaken only by rulemaking under the Administrative Procedures Act;⁶⁵ section 505(j) of the Act, on the other hand, includes no requirement that FDA engage in rulemaking prior to making a "sameness" determination. In the absence of express statutory language requiring rulemaking, government agencies possess broad discretion in deciding whether to proceed by general rulemaking or case-

⁶⁵ See *In re Bluewater Network*, 234 F.3d 1305 (D.C. Cir. 2000) (Coast Guard's failure to undertake any rulemaking mandated by Congress in the Oil Pollution Act of 1990 inconsistent with specific statutory requirement); see also *Becton, Dickinson & Co. v. FDA*, 448 F. Supp. 776 (N.D.N.Y.), *aff'd*, 589 F.2d 1175 (2nd Cir. 1978) (FDA must implement restricted device provisions through rulemaking).

by-case adjudication.⁶⁶ Courts have held that FDA may implement the ANDA approval provisions of the Act through individual adjudication.⁶⁷

VII. PETITIONS FOR STAY

In its petition for stay of action, GSK asks FDA to stay the approval of any approved ANDA or 505(b)(2) application, or decision to approve any new or pending ANDA or 505(b)(2) application, for a drug product that includes cefuroxime axetil in crystalline form until final resolution of the issues raised in its citizen petition. PDI (PDI Petition for Stay at 2) broadens this request slightly to include staying the approval of new or pending applications for a drug product that includes cefuroxime axetil with a different stereoisomeric mixture than that of Ceftin. Both petitioners request that, if FDA denies the petitions, the stay not expire until a reviewing court has ruled on the correctness of the decisions as long as the petitioner seeks court review within two weeks of its receipt of the adverse decision.

GSK maintains (Petition for Stay at 3-4) that it satisfies the requirements for a mandatory grant of a stay under 21 CFR 10.35(e)(1)-(4). GSK states that it will suffer irreparable injury because the reputation of Ceftin products will be diminished and GSK will lose sales to generic products. GSK states that its citizen petition shows that its case is not frivolous and is well grounded in applicable law, and the petitioner adds that it is pursuing this matter in good faith. GSK contends that it has demonstrated sound public policy grounds for a stay because it believes that permitting the marketing of cefuroxime axetil products containing crystalline drug substance would be contrary to law and could put patients at risk unless significant testing and tight acceptance criteria were required. Finally, GSK maintains that a stay would not be outweighed by public health or other public interest because it believes that there is no public interest in the marketing of products that are not clinically the same as the innovator product. PDI (PDI Petition for Stay at 4-6) presents very similar arguments in support of its request for a stay.

FDA will grant a stay only when *all* the provisions set forth in § 10.35(e)(1)-(4) have been satisfied.⁶⁸ FDA has carefully considered all the arguments raised and information provided in GSK's and PDI's citizen petitions and supplemental submissions. FDA denies GSK's and PDI's petitions for stay.

⁶⁶ *NLRB v. Bell Aerospace*, 416 U.S. 267, 293-94 (1974); *SEC v. Chenery Corp.*, 332 U.S. 194, 203 (1947); *Cellnet Communication, Inc. v. FCC*, 965 F.2d 1106, 1111 (D.C. Cir. 1992) ("an agency's refusal to initiate a rulemaking is evaluated with a deference so broad as to make the process akin to non-reviewability").

⁶⁷ *Teva Pharmaceuticals, USA, Inc. v. FDA*, 182 F.3d 1003, 1010 (D.C. Cir. 1999).

⁶⁸ Under § 10.35(e)(1)-(4), FDA will grant a stay of a proceeding if *all* of the following apply:

- (1) The petitioner will otherwise suffer irreparable injury.
- (2) The petitioner's case is not frivolous and is being pursued in good faith.
- (3) The petitioner has demonstrated sound public policy grounds supporting the stay.
- (4) The delay resulting from the stay is not [outweighed] by public health or other public interests.

FDA need not address the petitioners' claims that their cases are not frivolous and are being pursued in good faith, and that the petitioners would otherwise suffer irreparable injury, because the Agency concludes that the petitioners have not demonstrated sound public policy grounds for a stay. Furthermore, the Agency concludes that the potential delay resulting from the stay is outweighed by public health or other public interests.

FDA concludes that the public policy grounds presented by the petitioners do not support a stay of the approval of an ANDA for a generic cefuroxime axetil drug product containing cefuroxime axetil in wholly or partially crystalline form because, among other things, the approval of such a product would be consistent with the Act and FDA regulations. As discussed above, the Agency can, in full accord with the Act and FDA regulations, approve an ANDA for a cefuroxime axetil tablet product whose active ingredient is wholly or partially in crystalline form. FDA notes that the Agency receives deference in interpreting the Act,⁶⁹ the Agency also receives deference in interpreting its own regulations.⁷⁰ Generic drug approvals are within FDA's area of expertise, and FDA notes that it is due deference in making its scientific determinations.⁷¹ Moreover, FDA's approval of Ranbaxy's generic cefuroxime axetil product is consistent with longstanding policies; these policies have been consistently applied as demonstrated by other FDA approvals of generic drug products that contain a different physical form of the active ingredient than the physical form of the active ingredient in the reference listed drug. Longstanding policies consistently applied are also due deference.⁷²

Furthermore, the delay resulting from the stay would be outweighed by the public interest in receiving a safe and effective generic drug product. FDA concludes that Ranbaxy has met its burden of providing sufficient information in its ANDA to demonstrate that the cefuroxime axetil in its generic drug product is the "same" as the cefuroxime axetil in Ceftin. Ranbaxy has demonstrated that its product is bioequivalent to Ceftin and its product meets the other requirements necessary for approval; Ranbaxy's generic cefuroxime axetil drug product would pose no greater risk to patients than GSK's Ceftin. Because the petitioners have not met all the requirements for a stay under § 10.35(e)(1)-(4), FDA denies the petitions for stay.⁷³

⁶⁹ See *Chevron v. Natural Resources Defense Council, Inc.*, 467 U.S. 837 (1984).

⁷⁰ See *Martin v. Occupational Safety and Health Review Comm'n*, 499 U.S. 144, 150-51 (1991).

⁷¹ See *Bristol-Myers Squibb v. Shalala*, 923 F. Supp. 212, 220-21 (D.D.C. 1996); see also *Solite Corp. v. EPA*, 952 F.2d 473, 489-90 (D.C. Cir. 1991).

⁷² See *INS v. Cardoza Fonseca*, 480 U.S. 446, 488 n. 30 (1987).

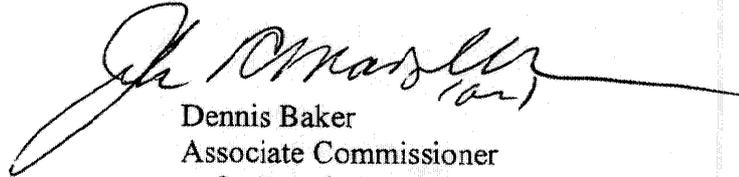
⁷³ Similarly, GSK is unlikely to succeed in obtaining a preliminary injunction in court because it cannot show that: (1) it has a substantial likelihood of success on the merits; (2) it will suffer irreparable injury in the absence of preliminary relief; (3) other interested parties will not suffer irreparable harm if the requested relief is granted; and (4) granting the relief is in the public interest. See *Serono Laboratories, Inc. v. Shalala*, 158 F.3d 1313, 1317-18 (D.C. Cir. 1998); *Bristol-Myers Squibb Co. v. Shalala*, 923 F. Supp. 212, 215 (D.D.C. 1996) (citing *Washington Metropolitan Area Transit Comm'n v. Holiday Tours, Inc.*, 559 F.2d 841, 843 (D.C. Cir. 1977)); *CityFed Fin. Corp. v. Office of Thrift Supervision*, 58 F.3d 738, 746 (D.C. Cir. 1995).

Docket Nos. 00P-1550/CP1 & PSA 1 and 01P-0428/CP1 & PSA1

VIII. CONCLUSION

For the reasons stated above, FDA denies the citizen petitions submitted by GSK and PDI, as well as their respective petitions for stay of action.

Sincerely yours,

A handwritten signature in black ink, appearing to read "Dennis Baker", with a long horizontal flourish extending to the right. The signature is written in a cursive style.

Dennis Baker
Associate Commissioner
for Regulatory Affairs