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November 7, 2001

VIA FEDERAL EXPRESS

Dockets Management Branch
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

Re: Citizen Petition Concerning Cefuroxime Axetil, Docket No. 00P-1550

Dear Sir or Madam:

In a document that accuses our client GlaxoSmithKline of delay, Ranbaxy Laboratories, Limited has now, more than thirteen months after the filing of the above-referenced citizen petition, filed its first public response to that petition.[1] Ranbaxy's submission misreads the precedents upon which it relies. FDA has in some cases treated different solid state forms of a chemical as the same active ingredient, such as with ranitidine hydrochloride, cefadroxil, and other circumstances in which different crystalline forms or different waters of hydration of pharmaceutical chemicals exist, "when dissolution, solubility, and absorption are shown to be equivalent." Letter from Carl C. Peck, M.D. to Thomas A. Hayes, M.D., Docket No. 90P-0240/CP, April 6, 1992 (cefadroxil decision), pg. 4 (copy attached as Exhibit U). Ranbaxy, in discussing FDA's historical approach, fails to address that important caveat. FDA has never approved an ANDA whose active ingredient differs from that of the innovator product in solid-state form in a situation, like that presented here, in which the two different forms are not

[1] The response generally raises no new arguments, but GlaxoSmithKline is constrained to respond to the Ranbaxy suggestion that GlaxoSmithKline's efforts to assure adherence to the law with respect to cefuroxime axetil are inappropriate "[g]iven the U.S. Government's and the American public's concerns that antibiotics may be in short supply due to the recent anthrax outbreaks." As FDA is aware, cefuroxime axetil is not indicated for the treatment of anthrax. GlaxoSmithKline has publicly offered to provide antibiotics that would be useful in the treatment of anthrax free to the United States Government for use by any affected person in this time of crisis. There is, in any case, no shortage of cefuroxime axetil or any other reason to approve Ranbaxy's product because of the bioterrorism attacks. Ranbaxy's efforts to exploit this issue for its own benefit are entirely inappropriate.

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interchangeable because they differ substantially in solubility and absorption. That material difference between crystalline cefuroxime axetil and amorphous cefuroxime axetil confirms that those two substances are different active ingredients. As different active ingredients, they cannot be combined and approved on the basis that the combination tests bioequivalent to the innovator's single ingredient product.

Respectfully submitted,

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DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service

Food and Drug Administration
Rockville MD 20857

APR 6 1992

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Thomas A. Hayes, M.D.
Director Regulatory Affairs
Bristol-Myers Squibb Co.
U.S. Pharmaceutical Group
Evansville, IN 47721-0001

Re: Docket No. 90P-0240/CP

Dear Dr. Hayes:

This letter responds to your July 13, 1990, citizen petition. Your petition requested that the Food and Drug Administration (FDA) deny approval of the pending applications submitted by Gema Liesa (Gema) and Zenith Laboratories (Zenith) for cefadroxil products. Your petition was followed by a letter, dated July 15, 1991, in which you pleaded for a timely response to your petition.

For the reasons stated below, we are denying your petition.

PETITIONER'S STATEMENT OF GROUNDS

Section 442.6 of the Code of Federal Regulations (21 CFR 442.6) sets forth standards (a monograph) for the identity, strength, quality, and purity found necessary to adequately ensure the safety and efficacy of products containing cefadroxil monohydrate and test methods to determine compliance with such standards. You state that the monograph for bulk cefadroxil monohydrate (21 CFR 442.6) specifies that the product must be a "monohydrate" and that its moisture content must be between 4.2 and 6.0 percent. You further state that the monographs for cefadroxil monohydrate capsules, tablets, and oral suspension (21 CFR 442.106a-c) incorporate by reference the requirements of the monograph for the bulk drug.

You assert that, based on an analysis of a sample of the bulk cefadroxil product manufactured by Gema and provided by Zenith to Bristol-Myers Squibb in a court proceeding, the product is not a monohydrate[1]. Therefore, it does not comply with the monograph at 21 CFR 442.6 and the applications for approval sought by Gema and Zenith must be denied.

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[1]FDA informed Bristol-Myers Squibb by letter of August 12, 1991, to Allan Fox, Esq., Attorney for Bristol-Myers Squibb Co., that the bulk drug substance manufactured by Gema is a hemihydrate. FDA's position on whether the Gema product conforms to the monograph for cefadroxil monohydrate is contained in this letter rather than that earlier preliminary response.

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Although you request denial of approval of specific applications, the basic issue raised by your petition is whether FDA can accept and approve an abbreviated antibiotic application for an antibiotic drug product whose only difference from an established monograph is a difference in water of hydration. Therefore, a decision on your request depends on FDA's resolution of this issue.

AGENCY RESPONSE

I. FDA's Authority to Approve Antibiotic Drugs

A. Statutory Authority

The statutory authority for approving antibiotics, including generic versions, is section 507 of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 357). To obtain the initial approval of a new antibiotic drug for human use, an applicant must file with FDA an application (Form 5) containing data showing the safety and effectiveness of the new antibiotic in accordance with section 507 of the act. Under section 507, approval of an antibiotic drug product by FDA results in the establishment of a monograph for the product, which is a regulation codified in the Code of Federal Regulations. An antibiotic monograph describes standards of identity, strength, quality, and purity that are necessary to assure the safety and efficacy of the drug, and test methods to determine compliance with such standards.

FDA has always approved a generic copy of an antibiotic (i.e., the same drug made by a different firm) upon a showing that the generic conformed to the specifications set out in the applicable monograph. In addition, as with generic copies of nonantibiotic drugs, generic copies of approved antibiotic drugs must also show bioequivalence to the approved antibiotic drug for which FDA has established a monograph. Historically, approval of a generic copy of an antibiotic drug has been obtained by the filing of a "Form 6," containing the same data as a Form 5, minus the basic safety and effectiveness testing.

Section 507(a) requires that FDA certify that each batch of an antibotic drug conform to the applicable monograph, unless FDA has exempted such drug from the certification process in accordance with section 507(c). Because of antibiotic drug manufacturers' high level of compliance with existing monographs, in 1982, FDA concluded that all classes of antibiotic drugs could be exempted from the batch certification requirements of section 507(a).[2] Pursuant to

[2]47 FR 39155 (1982)

section 507(e) of the act, these exempted antibiotics, upon approval, are subject to section 505 of the act. An approved antibiotic application (Form 5) is regarded as an approved new drug application (NDA) under § 314.50 (21 CFR 314.50) and an approved abbreviated antibiotic application (Form 6) is regarded as an abbreviated new drug application (ANDA) under § 314.55 (21 CFR 314.55).

As part of an effort to simplify procedural requirements, FDA now requires a similar application submission (Form FDA 356h) for antibiotics and nonantibiotics so that a former Form 5 equates with an NDA and a former Form 6 equates with an ANDA. In addition, for review purposes, FDA applies the same approval procedures to human antibiotic applications as to nonantibiotic applications.

B. Applicable Regulations

Section 314.56(e) (21 CFR 314.56(e)) provides that abbreviated applications are suitable for "duplicates of an antibiotic drug for which FDA has approved an application." Section 314.55(c)(1) (21 CFR 314.55(c)(1)) provides that "a finding by FDA that an abbreviated application is suitable for a drug product applies only to a product that is the same in active ingredient, dosage form and strength, route of administration, and conditions of use as the drug product that was the subject of the finding." In proposing this regulation, FDA stated that "the agency accepts antibiotic Form 6's . . . for all antibiotic drugs that are comparable to an antibiotic drug for which the agency's requlations provide for certification" (emphasis added).[3]

II. **Are Active Ingredients with Different Waters of Hydration Considered "Duplicates?"**

FDA has on several occasions stated its position on the meaning of "same" or "identical" active ingredient. In its proposed rule to implement Title I of the Drug Price Competition and Patent Term Restoration Act of 1984 (Pub. L. 98-417), FDA interpreted the statutory requirement that "the active ingredients in the proposed drug product be the same as that of the listed drug" to mean that the active ingredients must be identical, i.e., a different salt or ester of the active ingredient in the proposed drug product would not be identical to the active ingredient in the listed drug.[4] In its evaluation of pharmaceutical equivalence, FDA will not

[3]47 FR 46626 (1982)

[4]54 FR 28881 (1989)

evaluate two drug products as therapeutic equivalents if the products contain different salts or esters of the same therapeutic moiety; however, anhydrous and hydrated entities are not considered to be different salts or esters. Thus, in the case of ampicillin and ampicillin trihydrate, if they meet the same standards and their equivalence is supported by appropriate bioavailability/bioequivalence studies, FDA would consider them pharmaceutical equivalents.[5]

Cefadroxil hemihydrate is neither a salt nor an ester of cefadroxil monohydrate. The active moiety of each ingredient is cefadroxil, i.e., it is cefadroxil that achieves the intended effect in the diagnosis, cure, mitigation, treatment, or prevention of a disease or in affecting the structure or function of the human body (See 21 U.S.C. 321(g)(1)). FDA considers differences in waters of hydration resulting in polymorphic crystal forms of the same active moiety (i.e., different forms of the same active ingredient) to be the same when dissolution, solubility, and absorption are shown to be equivalent. Demonstration of such equivalence is a required part of the approval process for an abbreviated antibiotic application. On the other hand, esters or salts of the same active moiety are not considered the same active ingredient because they require metabolic conversion before the active moiety is made available. Therefore, a cefadroxil hemihydrate product would be considered a "duplicate" of a cefadroxil monohydrate product in accordance with the regulation at § 314.56(e). Consequently, FDA may accept and approve an abbreviated antibiotic application for cefadroxil hemihydrate if the applicant can meet all of the standards of the monohydrate monograph except the moisture content specification, and the applicant shows that its product is bioequivalent to the cefadroxil monohydrate product.

I do not, and cannot, comment on or imply that we have made any findings on Gema's and Zenith's applications. I simply conclude that you have not demonstrated sufficient reason to require FDA to deny approval of an abbreviated application for an antibiotic product whose only difference from an established monograph is its water of hydration.

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[5]44 FR 2950 (1979); Approved Drug Products with Therapeutic Equivalence Evaluations, 12th Edition (1992) at xii. The agency's position with respect to therapeutic equivalence and ingredients with different waters of hydration is a long-standing one. It did not evolve in the context of this petition concerning cefadroxil products. This is evidenced by FDA's conclusions about ampicillin and ampicillin trihydrate in establishing Maximum Allowable Costs (MAC's) for certain forms and strengths of ampicillin (41 FR 51087 (1976)).

CONCLUSION

For the reasons described above, your petition requesting FDA to deny approval of applications submitted by Gema and Zenith for their versions of cefadroxil is denied.

Sincerely yours,

Carl C. Peck, M.D.
Director
Center for Drug Evaluation
and Research

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