



RANBAXY
LABORATORIES LIMITED

SECTOR-18, UDYOG VIHAR INDUSTRIAL AREA, GURGAON-122001
PHONE: (91-124) 342001-10, Fax: (91-124) 342017, 342030

EXHIBIT

16
11/10/00 kmf

November 6, 2000

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 208955-2773

FAX AND UPS OVERNIGHT

FAX AMENDMENT

Reference: Cefuroxime Axetil Tablets 125 mg, 250 mg and 500 mg
ANDA 65-043
FAX Amendment

Dear Sir/Madam:

Reference is made to the pending ANDA 65-043 for Cefuroxime Axetil Tablets 125mg, 250mg and 500mg. Reference is also made to the Fax Deficiency dated October 12, 2000.

Ranbaxy's response to the deficiency questions is in the same order as requested.

FIELD COPY: This is to certify that the field copy is a true copy of the technical sections described in the 21 CFR 314.94 (d)(5), chemistry, manufacturing and controls section contained in the archival and review copies of the application.

If you have any questions, I can be reached at 609-720-5623 or Shirley TERNYIK can be reached at 609-720-5612. Thank you.

Sincerely,

Stephanie J. Davis

Stephanie J. Davis (for)
Shirley TERNYIK
US Agent for Ranbaxy Laboratories Limited

DEPARTMENT OF HEALTH AND HUMAN SERVICES
 FOOD AND DRUG ADMINISTRATION

**APPLICATION TO MARKET A NEW DRUG, BIOLOGIC,
 OR AN ANTIBIOTIC DRUG FOR HUMAN USE**

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved OMB No 0910-0338
 Expiration Date March 31, 2003
 See OMB Statement on page 2

FOR FDA USE ONLY
 APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT Ranbaxy Laboratories Limited	DATE OF SUBMISSION November 6, 2000
TELEPHONE NO. (include Area Code) 91-1246-342001	FACSIMILE (FAX) Number (include Area Code) (609)720-1155
APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued) Sector 18, Udyog Vihar Industrial Area Gurgaon - 122 001, INDIA	AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE Shirley Temyik, US Agent Ranbaxy Pharmaceuticals Inc. 600 College Road East Princeton, NJ 08540 (609) 720-5612

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (if previously issued) 65-043

ESTABLISHED NAME (e.g., Proper name, USP/USAN name) Cefuroxime Axetil Tablets	PROPRIETARY NAME (trade name) IF ANY NONE
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (if any)	CODE NAME (if any) N/A
DOSAGE FORM: Tablet	STRENGTHS 125mg, 250mg and 500mg
ROUTE OF ADMINISTRATION Oral	
(PROPOSED) INDICATION(S) FOR USE.	

APPLICATION INFORMATION

APPLICATION TYPE (check one) NEW DRUG APPLICATION (21 CFR 314.50) ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE 505 (b)(1) 505 (b)(2)

IF AN ANDA, or 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
 Name of Drug: Cefin®
 Holder of Approved Application: Glaxo Wellcome Inc.

TYPE OF SUBMISSION (check one) ORIGINAL APPLICATION AMENDMENT TO A PENDING APPLICATION RESUBMISSION
 PRESUBMISSION ANNUAL REPORT ESTABLISHMENT DESCRIPTION SUPPLEMENT EFFICACY SUPPLEMENT
 LABELING SUPPLEMENT CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT OTHER

IF A SUBMISSION OR PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY CBE CBE-30 Prior Approval (PA)

REASON FOR SUBMISSION
Fax Amendment

PROPOSED MARKETING STATUS (check one) PRESCRIPTION PRODUCT (Rx) OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED THIS APPLICATION IS PAPER PAPER AND ELECTRONIC ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
 Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g., Final dosage form, Stability/testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

JA 280

This application contains the following items: (Check all that apply)

<input type="checkbox"/>	1. Index		
<input type="checkbox"/>	2. Labeling (check one)	<input type="checkbox"/> Draft Labeling	<input type="checkbox"/> Final Printed Labeling
<input type="checkbox"/>	3. Summary (21 CFR 314.50(c))		
<input checked="" type="checkbox"/>	4. Chemistry section		
<input checked="" type="checkbox"/>	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)		
<input type="checkbox"/>	B. Samples (21 CFR 314.50(e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)		
<input type="checkbox"/>	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)		
<input type="checkbox"/>	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)		
<input type="checkbox"/>	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)		
<input type="checkbox"/>	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))		
<input type="checkbox"/>	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)		
<input type="checkbox"/>	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)		
<input type="checkbox"/>	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)		
<input type="checkbox"/>	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)		
<input type="checkbox"/>	12. Case report forms (e.g., 21 CFR 314.50(f)(2); 21 CFR 601.2)		
<input type="checkbox"/>	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))		
<input type="checkbox"/>	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355(b)(2) or (j)(2)(A))		
<input type="checkbox"/>	15. Establishment description (21 CFR Part 600, if applicable)		
<input type="checkbox"/>	16. Debarment certification (FD&C Act 306(k)(1))		
<input type="checkbox"/>	17. Field copy certification (21 CFR 314.50(k)(3))		
<input type="checkbox"/>	18. User Fee Cover Sheet (Form FDA 3397)		
<input type="checkbox"/>	19. Financial Information (21 CFR Part 54)		
<input type="checkbox"/>	20. OTHER (Specify)		

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT <i>Stephanie Davis</i>	TYPED NAME AND TITLE Stephanie Davis (for) Shirley Temyik U.S. Agent for Ranbaxy Laboratories	DATE November 6, 2000
ADDRESS (Street, City, State, and ZIP Code) Ranbaxy Pharmaceuticals Inc. 600 College Road East, Princeton, NJ 08540		TELEPHONE NUMBER (609)720-5612

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

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ANDA: 65-043 APPLICANT: Ranbaxy Laboratories Limited

DRUG PRODUCT: Cefuroxime Axetil Tablets, 125 mg, 250 mg and 500 mg

The deficiencies presented below represent FAX deficiencies.

A. Deficiencies:

1. The related substances specifications are not justified by the levels found in the bulk drug substances used in manufacture of the exhibit batches.

The related substances specifications of the bulk drug substances amorphous Cefuroxime Axetil and crystalline Cefuroxime Axetil have been reviewed in view of the available data. The following table reflects the revised related substances specifications.

Amorphous Cefuroxime Axetil

CONFIDENTIAL MATERIAL OMITTED

**MATERIAL SUBJECT TO PROTECTIVE ORDER
ENTERED DECEMBER 11, 2000 IN
CASE NO. 00-5172 (MLC) BEFORE THE
U.S. DISTRICT COURT FOR THE
DISTRICT OF NEW JERSEY**

DESCRIPTION OF MATERIAL OMITTED:

TECHNICAL INFORMATION
FROM RANBAXY'S ANDA

The revised drug substance specifications for amorphous and crystalline Cefuroxime Axetil are in Attachment 1.

2. We remain concerned regarding the drug product's potential for conversion to the crystalline form. Please demonstrate that you have adequately challenged the dosage form, e.g., by determining requisite conditions for conversion to crystalline form.

There are three areas which can lead to potential conversion to the crystalline form:

- A. API - Effect of aging on amorphous Cefuroxime Axetil
 - B. Manufacturing process of drug product
 - C. Stability of drug product
- A. API - Effect of aging on Amorphous Cefuroxime Axetil

We have 3 months accelerated and 9 months real time stability data on DMF batches of amorphous Cefuroxime Axetil. This data reveals that there is no conversion to crystalline form as amorphous Cefuroxime Axetil did not show any birefringence or extinction positions at any stability station.

CONFIDENTIAL MATERIAL OMITTED

**MATERIAL SUBJECT TO PROTECTIVE ORDER
ENTERED DECEMBER 11, 2000 IN
CASE NO. 00-5172 (MLC) BEFORE THE
U.S. DISTRICT COURT FOR THE
DISTRICT OF NEW JERSEY**

DESCRIPTION OF MATERIAL OMITTED:

TECHNICAL INFORMATION
FROM RANBAXY'S ANDA

CONFIDENTIAL MATERIAL OMITTED

**MATERIAL SUBJECT TO PROTECTIVE ORDER
ENTERED DECEMBER 11, 2000 IN
CASE NO. 00-5172 (MLC) BEFORE THE
U.S. DISTRICT COURT FOR THE
DISTRICT OF NEW JERSEY**

DESCRIPTION OF MATERIAL OMITTED:

**TECHNICAL INFORMATION
FROM RANBAXY'S ANDA**

d. Compression of Tablets:

The percentage crystallinity was recorded in the final blend ready for compression and for the tablets. There was no significant change in percentage crystallinity observed during compression process indicating no significant change from the crystalline form

Also, we agree to the Agency's recommendation for inclusion of an acceptance range for the crystallinity test in our In-Process specification.

3. **Please provide an acceptance range for your in-process crystallinity test.**

The acceptance range for in-process crystallinity test is: 10-15%. The revised in-process specifications are in Attachment 2.

4. **Please include a test and specification for crystallinity in your finished and stability product testing protocols.**

The crystallinity limit of 10-15% has been included in the finished product specifications and in the stability specifications. The revised specifications for the finished product and stability are in Attachment 3 and Attachment 4 respectively.

5. **Please provide updated finished and stability product testing protocols to indicate use of the dissolution method and specifications recommended by the Division of Bioequivalence.**

The revised specifications for the finished product and stability in Attachment 3 and Attachment 4 include the dissolution method and specifications as recommended by the Division of Bioequivalence.

6. **The related substances specifications for finished and stability product are not justified by the exhibit batch data provided.**

We have reviewed the finished product and stability data of the exhibit batches in view of the existing related substances specifications. The specifications have been revised based on the actual data obtained in the exhibit batches. The following table provides the revised related substances limits.

B. In addition to responding to the above deficiencies, please note and acknowledge the following in your response.

You should be aware that the revision to the monograph for Cefuroxime Axetil and Cefuroxime Axetil Tablets in the Sept. Oct. 2000 Pharmacopoeial Forum are proposed in-process revisions, and that the monograph as they appear in USP 24 remain official until such time as the proposed revision becomes official.

Ranbaxy notes and acknowledges that the USP requirements for cefuroxime axetil are currently as stated by the FDA in its Part B. However, Ranbaxy urges the FDA to consider the following in assessing the approvability of Ranbaxy's Cefuroxime Axetil product even prior to the anticipated revision of the USP.

1. Based on data submitted by Ranbaxy, the USP has proposed a revision of the monograph for cefuroxime axetil to include the crystalline form.

In FDA's Major Amendment Deficiency letter dated December 2, 1999, FDA requested that Ranbaxy petition the USP to revise the description of the drug substance, cefuroxime axetil. In fact, anticipating this, Ranbaxy had already petitioned the USP on September 11, 1998, requesting that the crystalline form of cefuroxime axetil be added to the USP monograph in addition to the amorphous form presently described in the monograph. In response to this initial request and after considerable correspondence and consideration, the USP notified Ranbaxy on June 7, 2000 that they are proposing to recognize the crystalline form of cefuroxime axetil, as we requested.

The revision will add one sentence to accommodate the crystalline form in the monograph. Presently, the USP states that if the particles do not show birefringence or exhibit extinction positions, it is amorphous. The complete proposed sentence will read "Particles that do not show birefringence or exhibit extinction positions are amorphous, and particles that show birefringence and exhibit extinction positions are crystalline." See In-Process Revision, *Pharmacopoeial Forum*, Sept.-Oct. 2000, at 1277. In addition, the USP has proposed a dissolution specification change for 500 mg tablets.

Ranbaxy's Cefuroxime Axetil meets all current USP monograph tests and specifications except the crystallinity specification described above. This includes the identification test via USP's procedure under section <197> to use acetone as a solvent in the infrared spectra to dissolve the standard and test specimen of different forms. Ranbaxy is confident that the USP will eventually revise the monograph, as it has proposed. We maintain that OGD's review and approval of Ranbaxy's ANDA should continue and conclude, independent of the USP revision process.

2. The pendency of the USP monograph revision should not affect FDA's review and approval of Ranbaxy's ANDA.

FDA's regulations do not require that an ANDA must be based on an active ingredient that conforms to an existing USP monograph. See 21 C.F.R. § 314.94(a)(5)(a). Rather, the ANDA need only reference a "listed drug" that has been previously approved by FDA, such as Glaxo's Cefitin® (cefuroxime axetil). *Id.* Therefore, FDA can approve Ranbaxy's ANDA before the USP monograph is finalized and address the situation by requiring appropriate labeling information. Furthermore, a non-USP designation for Ranbaxy's product will not affect FDA's approval authority since the listed drug does not label its product as "USP." See section V of ANDA No. 65-043.

3. There is no scientific reason for USP to decline to implement the monograph revision.

Ranbaxy has provided sufficient information to the USP to facilitate the revision of the cefuroxime axetil monograph to include the crystalline form of the active ingredient.

Moreover, the USP reference standard (likely from Glaxo) contains some traces of crystalline cefuroxime axetil. See, attached photomicrograph of the USP reference standard material (lot F-1), as tested by Ranbaxy as supplied in Attachment-6. This photomicrograph shows the presence of some crystals in the allegedly purely amorphous Glaxo material. The presence of crystallinity is consistent with Glaxo's patent United States Patent No. 4,562,181, wherein Glaxo itself describes 4 different preparations of cefuroxime axetil containing from a "few crystals" to 10% crystallinity (Ex. 22 of United States Patent No. 4,562,181 as described by Glaxo in its correspondence with the Patent & Trademark Office in the prosecution of a related patent United States Patent No. 5,013,833). In its September 29, 2000 Citizen Petition, Glaxo states that a cefuroxime axetil (crystalline) product will not be "entirely or predominantly in amorphous form." It is possible that Glaxo uses these terms in an attempt to evade the fact that Cefitin® is not a pure amorphous form of cefuroxime axetil but, in fact, contains some crystallinity. The testing of the USP material would seem to confirm this. Also, for comparison, please note that Glaxo does not label its product Cefitin's® as "USP". In other words, Cefitin's® active ingredient, in some instances may include a small amount of the crystalline form of cefuroxime axetil, just like Ranbaxy's active ingredient (which is 88% amorphous and 12% crystalline, see section VII of ANDA No. 65-043).

Glaxo's patent documents also disclose the fact that several of its product manufacturing and processing techniques - including spray drying, freeze drying, and solvent precipitation - produce amorphous forms of cefuroxime axetil necessarily having varying degrees of crystallinity. Given these facts, there is every scientific reason for the agency to approve the Ranbaxy ANDA while the USP is revising the monograph to describe both amorphous and crystalline forms of cefuroxime axetil.

4. Ranbaxy's ANDA provides data that establishes the necessary requirements for approval under 21 U.S.C. § 355(j).

As required by 21 U.S.C. § 355(j), Ranbaxy's ANDA contains information to show that its cefuroxime axetil product contains the same active ingredient, route of administration, dosage form, strength, and labeling as the listed drug, and that its product is bioequivalent to the listed drug. At this point, we reference a September 29, 2000 Citizen Petition and Petition for Stay of Action submitted to FDA by Glaxo Wellcome Inc. (FDA Docket No. 00P-1550). These petitions question FDA's authority to approve Ranbaxy's ANDA for Cefuroxime Axetil tablets. Although Ranbaxy's present response to FDA's October 12, 2000 Fax Amendment should not be considered a definitive reply to the Glaxo petitions, we provide the following information to verify that Ranbaxy's ANDA does, in fact, meet all of the necessary approval requirements.

a. Ranbaxy's product contains the same active ingredient as the listed drug.

- (1) FDA interprets "active ingredient" to include the active moiety's various crystalline/polymorphic forms.

Glaxo's petition implies that Ranbaxy's Cefuroxime Axetil tablets do not contain the same active ingredient as Cefin® because Ranbaxy's active ingredient is not "entirely or predominantly in amorphous form," as is Cefin®. See Glaxo Citizen Petition at 3-5. Glaxo's assertions are disingenuous for two reasons. First, as described above, Cefin® does, in fact, contain a certain amount of cefuroxime axetil in crystalline form; hence, Glaxo's carefully chosen description that Cefin® contains a "predominantly" amorphous form of the active ingredient. Second, FDA has acknowledged for at least 25 years that the active moiety of a drug substance can be present in one of several crystalline forms - whether amorphous or polymorphous. Thus, Glaxo's "predominantly" amorphous form and Ranbaxy's crystalline form represent two physical forms of the same active ingredient in almost identical physical forms.

When interpreting the statutory requirement that an ANDA product contain the "same" active ingredient as the listed drug, FDA determined that a product's active ingredient is the same if it contains the identical salt or ester of the same active moiety. See 54 Fed. Reg. 28881 (1989). Amorphous and polymorphous entities are not different salts or esters but, rather, constitute different physical forms of the same active moiety. FDA applied this scientific position to drug products with different crystalline forms as early as 1987. Specifically, FDA determined that, "[s]ome drug substances exist in several different crystalline forms ('polymorphs'), due to a different arrangement of molecules in the crystal lattice, which thus show distinct differences in their physical properties. The same drug substance may also exist in a noncrystalline (amorphous) form. These various forms differ in their thermodynamic energy content, but not in composition." FDA's "Guideline for Submitting Supporting Documentation in Drug Applications for the Manufacture of Drug Substances" (Feb. 1987), at 46-47 (emphasis added).

Not only are they the same active ingredient but also can form the basis for a therapeutically equivalent generic drug product. In its extensive discussion on therapeutic equivalence determinations, FDA explains that "[d]ifferent salts and esters of the same therapeutic moiety are regarded as pharmaceutical alternatives. . . . Anhydrous and hydrated entities, as well as different polymorphs, are considered pharmaceutical equivalents and must meet the same standards and, where necessary, as in the case of ampicillin/ampicillin trihydrate, their equivalence is supported by appropriate bioavailability/bioequivalence studies." FDA's Approved Drug Products With Therapeutic Equivalence Evaluations ("the Orange Book"), at Preface, Section 1.7 (emphasis added). Thus, cefuroxime axetil amorphous and cefuroxime axetil crystalline represent two forms of the same active ingredient.

- (2) FDA has approved ANDAs for generic drugs that contain a different crystalline/polymorphic form than the listed drug.

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

Specifically, Bristol-Myers Squibb (BMS) raised an issue similar to Glaxo's claim in a 1990 citizen petition. BMS marketed an antibiotic drug, cefadroxil monohydrate capsules. Zenith Laboratories (Zenith) sought FDA approval for a generic version of cefadroxil monohydrate capsules, with the bulk active ingredient manufactured by Gema Liesa. An antibiotic monograph for bulk cefadroxil monohydrate set forth standards for the identity, strength, quality and purity of the drug substance, including a moisture content of between 4.2 and 6.0 percent. BMS alleged that the ingredient manufactured by Gema Liesa and referenced in the Zenith application was not a monohydrate and did not conform to the monograph's moisture content. As a monohydrate form of the antibiotic, BMS' cefadroxil contained one molecule of internally-bound water for every molecule of cefadroxil within the crystalline structure, to constitute approximately 4.7 percent of the substance. Zenith's cefadroxil, by contrast, was comprised of mostly adventitious (i.e., surface) rather than internally-bound water and, thus, was a hemihydrate. As such, Zenith's cefadroxil did not contain the same crystalline structure as the BMS product. In its citizen petition, BMS asserted that FDA should deny approval of the abbreviated drug application submitted by Zenith because the drug was not "the same" as the reference listed drug. See BMS Citizen Petition and accompanying attachments, dated July 13, 1990 (FDA Docket No. 90P-0240).

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

Ultimately, FDA denied the BMS petition on April 6, 1992. After a scientific review, FDA determined that the anhydrous form of an active ingredient constitutes the "same" active ingredient as the hydrated form, albeit with a different physical form, for purposes of Sections 505 and 507 of the Federal Food, Drug, and Cosmetic Act (FDCA). In so doing, FDA explained that this position with respect to the therapeutic equivalence of ingredients with different waters of hydration was a long-standing one, dating back at least to 1976 (citing 41 Fed. Reg. 51087 (1976) and 44 Fed. Reg. 2950 (1979)). The agency deduced that the active moiety of both forms was cefadroxil, and that the intended clinical effect of the drug was tied to the cefadroxil and was unaffected by the hydration form.

In conclusion, the agency stated, "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." FDA letter from Carl C. Peck, M.D., Director, Center for Drug Evaluation and Research, to Thomas A. Hayes, M.D., Director of Regulatory Affairs, Bristol-Myers Squibb Co., dated April 6, 1992, at 4 (FDA Docket No. 90P-0240). FDA further concluded that it had authority to approve an abbreviated application if the product met all of the standards of the monograph except for moisture content specification and the product was bioequivalent to the listed drug. FDA subsequently approved the generic cefadroxil product with labeling that referenced cefadroxil hemihydrate in place of the listed drug references to cefadroxil monohydrate. The agency later revised the antibiotic monograph to set standards for the identity, strength, quality and purity of cefadroxil hemihydrate.

Glaxo itself is well aware of the FDA's scientific position that distinctive crystalline forms encompass the same active ingredient. In November 1994, FDA tentatively approved an ANDA containing a Form 1 crystalline of ranitidine hydrochloride. In so doing, FDA determined that the Form 1 crystalline was "the same active ingredient" as the listed drug, Glaxo's Zantac®, which contained a Form 2 crystalline of ranitidine hydrochloride. After several lawsuits alleging patent infringement, Novopharm and Boehringer Ingelheim were permitted to sell FDA-approved equivalent versions of ranitidine hydrochloride containing the Form 1 crystalline. See Glaxo Inc. v. Novopharm Ltd., 110 F.3d 1562 (Fed. Cir. 1997); Glaxo Inc. v. Boehringer Ingelheim Corp., 1997 U.S. App. LEXIS 16954 (Fed. Cir. June 4, 1997). Given Glaxo's extensive knowledge of the scientific issues undergirding the ranitidine suits, we question whether the present petitions are sincere or merely a ploy to delay FDA's review process for a drug product that will compete directly with Glaxo's product.

b. Ranbaxy's product is bioequivalent to the listed drug.

Given the statutory requirement for bioequivalence, in conjunction with FDA's scientific position on the crystalline forms of drug substances, it is clear that Ranbaxy's ANDA can be approved on the basis of scientific data that establishes its bioequivalence to Glaxo's Cefitin®. Ranbaxy's evidence of bioequivalence is set forth in section VI of ANDA 65-043.

Furthermore, Ranbaxy's dissolution and stability testing establishes that the percentage of crystalline and amorphous forms in its tablets (12% and 88%, respectively) does not adversely affect the identity, strength, quality, purity, potency and performance of the drug product. See sections XII, XV, XVII of ANDA 65-043. In particular, the percentage of crystalline component in Ranbaxy's tablets shows no adverse impact on the solubility or in-vivo characteristics of the drug product, since the drug product complies with the bioequivalence criteria. The dissolution compliance has further been validated through a number of bioavailability studies conducted during the product development cycle using different percentages of crystalline component ranging from 10% to 20%, all of which showed complying bioequivalence characteristics. Based on the bioequivalence data available, it can be conclusively stated that the formulation with the crystalline component, even up to 20%, is bioequivalent to the Cefitin® tablets, refer to **Attachment-7**. Nevertheless, Ranbaxy's formulation includes the lower margin of only 12% crystalline component, leaving no probability that the crystalline component will adversely effect the quality of the product with respect to *in vivo* performance.

Additionally, Ranbaxy has evaluated the percentage of crystallinity of the drug product during aging/stability studies. Ranbaxy's formulation has been manufactured, released and tested for stability over a period of 18 months for the formulation (using formic acid, refer to **Attachment-8**) and 9 months for the formulation (using acetic acid, refer to **Attachment-5**). Based on the data generated, we have concluded that the level of crystalline component remains within the acceptance range of 10%-15% and does not show any potential for increase during stability testing.

The data contained in Ranbaxy's ANDA, and supplemented herein under Deficiency A, refutes Glaxo's insinuation that there is a need for additional "significant testing" of Ranbaxy's product prior to approval. See Glaxo Petition for Stay at 3. Moreover, Ranbaxy's bioequivalence data refutes Glaxo's unfounded product quality and therapeutic effect allegations. See id. In particular, any purported concern for the public health alleged by Glaxo because the generic product would not be "clinically the same" as Cefitin® is refuted in this case since Ranbaxy's bioequivalence data establishes that Ranbaxy's tablets will have an equivalent clinical effect as Glaxo's tablets. In sum, Glaxo has merely raised general questions about the data in Ranbaxy's application – sight unseen – that FDA would consider as a matter of course during its ANDA review process for a generic drug. Thus, there is no basis for FDA to delay the review process for Ranbaxy's Cefuroxime Axetil in response to the Glaxo petitions and, ultimately, the petitions should be denied.

c. **Ranbaxy's product labeling will be the same as the labeling for the listed drug.**

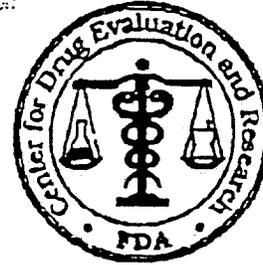
The FDCA requires that an ANDA contain information to show that the labeling for the generic drug is the same as the labeling approved for the listed drug. 21 U.S.C. § 355(j)(2)(A)(v). The requirement allows for an important exception, however – for changes required because the ANDA drug and the listed drug are produced or distributed by different manufacturers. *Id.* The term “produce” contemplates differences in formulation. FDA’s interpretation goes even further, declaring that an ANDA may contain differences in labeling that include differences in expiration date, formulation, bioavailability, or pharmacokinetics. 21 C.F.R. § 314.94(a)(8)(v). Thus, so long as Ranbaxy’s active ingredient, route of administration, dosage form and strength are the same as the listed drug, labeling information that describes the generic drug’s production or formulation may differ from the listed drug. As noted above, Ranbaxy’s crystalline form of cefuroxime axetil represents the same active ingredient as Glaxo’s “predominantly anhydrous” form, and any labeling changes necessary to reflect the difference in physical form are minimal and permissible. In addition, as described above, FDA previously has incorporated similar differences in the labeling of generic drugs with crystalline forms that vary from the listed drug.

FAX AMENDMENT

OCT 12 2000

ANDA 65-043

OFFICE OF GENERIC DRUGS, CDER, FDA
 Document Control Room, Metro Park North II
 7500 Standish Place, Room 150
 Rockville, MD 20855-2773 (301-594-0320)



TO: APPLICANT: Rambaxy Laboratories Limited

TEL: 609-720-5612

ATTN: Shirley Ternyk

FAX: 609-720-1155

FROM: Mark Anderson

PROJECT MANAGER: 301-827-5848

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated April 19, 1999, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Cefuroxime Axetil Tablets, 125 mg, 250 mg, and 500 mg.

Reference is also made to your amendments dated March 1, March 7, July 27, July 31, August 2, and August 28, 2000.

Attached are 2 pages of minor deficiencies and/or comments that should be responded to within 30 calendar days from the date of this document. This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed. Your complete response should be (1) faxed directly to our document control room at 301-827-4337; (2) mailed directly to the above address, and (3) the cover sheet should be clearly marked a FAX AMENDMENT.

Please note that if you are unable to provide a complete response within 30 calendar days, the file on this application will be closed as a MINOR AMENDMENT and you will be required to take an action described under 21 CFR 314.170 which will either amend or withdraw the application. Accordingly, a response of greater than 30 days should be clearly marked MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. Facsimiles or incomplete responses received after 30 calendar days will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. You have been/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. Further if a major deficiency is cited in the bioequivalence review, the subsequent Not Approvable letter will request that the reply be declared a MAJOR AMENDMENT.

SPECIAL INSTRUCTIONS:

Chemistry comments are provided.

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, OR PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

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MA

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OCT 12 2000

38. Chemistry Comments to be Provided to the Applicant

ANDA: 65 043 APPLICANT: Ranbaxy Laboratories Limited

DRUG PRODUCT: Cefuroxime Axetil Tablets USP, 125 mg,
250 mg, and 500 mgThe deficiencies presented below represent FAX
deficiencies.

A. Deficiencies:

1. The related substances specifications are not justified by the levels found in the bulk drug substances used in manufacture of the exhibit batches.
2. We remain concerned regarding the drug product's potential for conversion to the crystalline form. Please demonstrate that you have adequately challenged the dosage form, e.g., by determining requisite conditions for conversion to crystalline form.
3. Please provide an acceptance range for your in-process crystallinity test.
4. Please include a test and specification for crystallinity in your finished and stability product testing protocols.
5. Please provide updated finished and stability product testing protocols to indicate use of the dissolution methods and specifications recommended by the Division of Bioequivalence.
6. The related substances specifications for finished and stability product are not justified by the exhibit batch data provided.
7. Please provide the individual tablet data for your stability dissolution studies, or indicate the range of the individual tablet data.

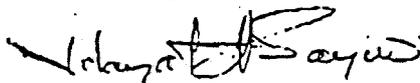
JA 294

R 5972

- B. In addition to responding to the above deficiencies, please note and acknowledge the following in your response:

You should be aware that the revisions to the monographs for Cefuroxime Axetil and Cefuroxime Axetil Tablets in the Sept. Oct. 2000 Pharmacopeial Forum are proposed in-process revisions, and that the monographs as they appear in USP 24 remain official until such time as the proposed revision becomes official.

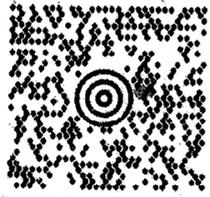
Sincerely yours,



Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

JA 295

R 5973



MD 207 9-04



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