DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

ANDA 077830
ANDA 078078

Ranbaxy Inc.
U.S. Agent for Ranbaxy Laboratories Limited
Attention: Sameer Manan
Director Regulatory Affairs
600 College Road East
Princeton, NJ 08540

Dear Mr. Manan:

This is in reference to your abbreviated new drug applications (ANDAs), submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the FD&C Act), for Esomeprazole Magnesium Delayed-release Capsules, 20 mg and 40 mg (ANDA 077830), and Valganciclovir Hydrochloride Tablets USP, 450 mg (ANDA 078078).

Upon review of our records, we have determined that FDA erred in tentatively approving ANDA 077830 on February 5, 2008, and ANDA 078078 on June 20, 2008. As described in detail below, FDA granted tentative approval to these ANDAs while the compliance status of one or more of the facilities referenced in the applications was unacceptable to support tentative approval. Accordingly, with this letter we are rescinding our previously granted tentative approval letters.[1] As a result of these rescissions, we also have determined that Ranbaxy[2] has forfeited its eligibility for 180-day exclusivity for its ANDA for Valganciclovir Hydrochloride Tablets USP, 450 mg (ANDA 078078).[3] We have arrived at this determination because Ranbaxy

[1] FDA notes that the Agency may have erroneously granted tentative approval to other Ranbaxy ANDAs on the same basis. This letter is limited to those ANDAs for which the submission date is the same as the date on which the first substantially complete ANDA containing a certification described in section 505(j)(2)(A)(vii)(IV) was submitted to FDA, according to the list of Paragraph IV Patent Certifications, and for which rescission of tentative approval has the potential to eliminate a block to approval for subsequent applicants . The Paragraph IV Patent Certifications list is available at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/ucm047676.htm.

[2] In this letter, we use the term "Ranbaxy" to refer to Ranbaxy Inc., Ranbaxy Laboratories Limited, and other related entities, collectively or individually.

[3] FDA's policy is generally not to decide an applicant's eligibility for 180-day exclusivity until the first applicant or a subsequent ANDA is ready for approval. See, e.g., Letter to W. Rakoczy, Rakoczy, Molino, Mazzochi & Siwik, LLP fr. G. Buehler, Director, FDA Office of Generic Drugs re. Docket No. FDA-2007-P-0249, Exhibit 1, at 1, note 1 (May 7, 2008). Consistent with this policy, FDA has not made any determination regarding Ranbaxy's eligibility for 180-day exclusivity for its ANDA for Esomeprazole Magnesium Delayed-release Capsules, 20 mg and 40 mg (ANDA 077830).

failed to obtain tentative approval of this ANDA within 30 months after the date on which this ANDA was submitted and such failure was not caused by a change in or a review of the requirements for approval.

I. STATUTORY BACKGROUND

A. ANDA Approval and Tentative Approval

The Drug Price Competition and Patent Term Restoration Act of 1984 (Public Law 98-417) (the Hatch-Waxman Amendments) created section 505(j) of the FD&C Act, which established the ANDA approval process for generic drugs.[4] To obtain approval, an ANDA applicant is not required to provide independent evidence of the safety and effectiveness of the proposed generic drug product. Instead, the applicant relies on FDA's previous finding that the listed drug referenced in the ANDA (reference listed drug or RLD) is safe and effective.[5] The ANDA applicant must identify the listed drug on which it seeks to rely and, with limited exceptions, a drug product described in an ANDA must contain the same active ingredient, conditions of use, route of administration, dosage form, strength, and (with certain permissible differences) labeling as the listed drug it references.[6] The ANDA applicant also must demonstrate that its proposed generic drug is bioequivalent to the RLD it references.[7]

In addition to the foregoing, an ANDA applicant must demonstrate that it complies with the current good manufacturing practice (CGMP) regulations. In particular, section 505(j)(2)(A)(vi) of the FD&C Act requires an ANDA to include "the items specified in clauses (B) through (F) of subsection (b)(1)," which include "a full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug."[8] Similarly, section 505(j)(4)(A) of the FD&C Act, which provides the bases on which an ANDA may not be approved, states the Secretary shall not approve an ANDA if, "the methods used in, or the facilities and controls used for, the manufacture, processing, and packing of the drug are inadequate to assure and preserve its identity, strength, quality, and purity." FDA's regulations

[4] *Drug Price Competition and Patent Term Restoration Act of 1984*, Pub. L. No. 98-417, 98 Stat. 1585.

[5] A RLD is "the listed [i.e., approved] drug identified by FDA as the drug product upon which an applicant relies in seeking approval of its abbreviated application" (21 CFR 314.3).

[6] Sections 505(j)(2)(A) and (j)(4) of the FD&C Act. See also 21 CFR 314.94(a). To submit an ANDA for a drug product which is not identical to a listed drug in route of administration, dosage form, and strength, or in which one active ingredient is substituted for one of the active ingredients in a listed combination drug, an applicant must first obtain permission from FDA through a petition submitted pursuant to section 505(j)(2)(C) of the FD&C Act and 21 CFR 314.93.

[7] See, e.g., section 505(j)(2)(A)(iv) of the FD&C Act (requiring "information to show that the new drug is bioequivalent to the listed drug).

[8] Section 505(b)(1)(D) of the FD&C Act.

reflect these requirements,[9] and provide greater detail on requirements with respect to demonstrating CGMP compliance.[10]

If FDA determines that it cannot approve an ANDA in its present form for one or more of the reasons given in 21 CFR 314.127, FDA will send the applicant a "complete response" letter that describes the specific deficiencies that the agency has identified in an ANDA.[11] If FDA decides to disapprove an application, FDA must provide the applicant notice of an opportunity for a hearing before it on the question of whether such application is approvable.[12]

FDA will tentatively approve an ANDA that meets the substantive requirements for approval, but cannot be fully approved due to existing patents or exclusivities. In particular, the statute defines "tentative approval" as a "notification to an applicant by the Secretary that an application under this subsection meets the requirements of paragraph (2)(A), but cannot receive effective approval *because* the application does not meet the requirements of this subparagraph, there is a period of exclusivity for the listed drug under subparagraph (F) or section [505A of the FD&C Act], or there is a 7-year period of exclusivity for the listed drug under section [527 of the FD&C Act]."[13] The statute also provides that "[a] drug that is granted tentative approval by the Secretary is not an approved drug and shall not have an effective approval until the Secretary issues an approval after any necessary additional review of the application."[14]

The "requirements of this subparagraph" in section 505(j)(5)(B)(iv)(II)(dd)(AA) refer to the patent certification requirements, 30-month stay, 180-day exclusivity,[15] and associated requirements related to timing of approvals described in subparagraph 505(j)(5)(B) of the FD&C Act. Thus, under the terms of the statute, tentative approval is appropriate when the reason an application cannot receive full effective approval is, for instance, that the reference listed drug has unexpired patent or exclusivity rights. Tentative approval is not appropriate where there are additional reasons unrelated to patents or exclusivity (such as failure to have adequate compliance with CGMP) that would prevent an application from receiving a full, effective approval.

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[9] See 21 CFR 314.94(a)(9)(i); 314.127(a)(1) (stating FDA will refuse to approve an ANDA if "[t]he methods used in, or the facilities and controls used for, the manufacture, processing, and packing of the drug product are inadequate to ensure and preserve its identity, strength, quality, and purity.").

[10] 21 CFR Parts 210, 211.

[11] 21 CFR 314.110(a). We note that at the time of tentative approval, FDA sent "not approvable" letters in such circumstances, the regulatory precursor to the "complete response" letter. That change in practice, codified in July 2008, is not material to the instant issues. *Applications for Approval to Market a New Drug; Complete Response Letter; Amendments to Unapproved Applications; Final Rule*, 73 FR 39588-01 (July 10, 2008),

[12] Section 505(j)(5)(E) of the FD&C Act.

[13] Section 505(j)(5)(B)(iv)(II)(dd)(AA) of the FD&C Act (emphasis added).

[14] Section 505(j)(5)(B)(iv)(II)(dd)(BB) of the FD&C Act.

[15] The FD&C Act provides certain ANDA applicants the opportunity to be the only generic drug manufacturer to compete with the innovator for a 180-day period. The requirements for obtaining and retaining this 180-day exclusivity period are described at sections 505(j)(5)(B)(iv) and 505(j)(5)(D) of the FD&C Act.

"Tentative approval" under section 505(j)(5)(B)(iv)(II)(dd) not only requires the submission of information purporting to describe manufacturing methods, facilities, and controls set out in section 505(b)(1)(D), but also requires the ability to demonstrate that the manufacturing methods, facilities, and controls described in the ANDA are adequate to assure and preserve the drug's identity, strength, quality, and purity.[16] To interpret this provision otherwise would require FDA to tentatively approve a product even when FDA knew that the product, if fully approved, would be deemed adulterated because it was made in a facility that did not comply with CGMP.[17] Notably, courts consistently have recognized that tentative approval is available only when an ANDA has met all the substantive requirements for approval, but is blocked from full effective approval by patent or exclusivity rights.[18]

We note that if the substantive standards for approval and for tentative approval were different, then the exception to forfeiture of 180-day exclusivity in section 505(j)(5)(D)(i)(IV) of the FD&C Act[19] in which a failure to obtain tentative approval in 30 months is excused if "the

[16] See, e.g., 21 CFR 314.105(d) ("FDA will approve an abbreviated new drug application and send the applicant an approval letter if none of the reasons in 314.127 for refusing to approve the abbreviated new drug application applies. The approval becomes effective on the date of the issuance of the agency's approval letter unless the approval letter provides for a delayed effective date. An approval with a delayed effective date is tentative and does not become final until the effective date."). We also note that Ranbaxy expressly has been notified of this practice in standard language included in FDA's tentative approval letters. See, e.g., Tentative Approval Letter to Ranbaxy Inc. fr. G. Buehler, Director, FDA Office of Generic Drugs re. ANDA 077472 for Cetirizine Hydrochloride Syrup, 5 mg/5 mL, (Nov. 1, 2006) ("We have completed the review of this ANDA, and based upon the information you have presented to date we have concluded that the drug is safe and effective for use as recommended in the submitted labeling. However, we are unable to grant final approval to your ANDA at this time because of the patent issue noted below. Therefore, the ANDA is **tentatively approved**. This determination is based upon information available to the agency at this time (i.e., information in your ANDA and the status of current good manufacturing practices (cGMPs) of the facilities used in the manufacturing and testing of the drug product).") (emphasis in original).

[17] See section 501(a)(1)(B) of the FD&C Act, which provides that "[a] drug . . . shall be deemed to be adulterated . . . if it is a drug and the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with current good manufacturing practice to assure that such drug meets the requirements of this Act as to safety and has the identity and strength, and meets the quality and purity characteristics, which it purports or is represented to possess."

[18] *AstraZeneca Pharms. LP v. FDA*, 850 F. Supp. 2d 230, 235 (D.D.C. 2012) ("[I]f the FDA finds that the generic drug satisfies the requirements for approval at the time of review, but final approval is blocked by a stay, a marketing exclusivity period, or some other barrier, the FDA will give the drug 'tentative approval.' 21 U.S.C. § 355(j)(5)(B)(iv)(II)(dd)(AA)."); *Mylan Pharms., Inc. v. Sebelius*, 856 F. Supp. 2d 196, 201 n.3 (D.D.C. 2012) (same); *Seattle Children's Hospital v. Akorn, Inc.*, Civil No. 10-5118, 2011 U.S. Dist LEXIS 145998, at *26 n.5 (N.D. Ill. Dec. 20, 2011); ("The FDA grants 'tentative' approval when an ANDA meets all of the technical, safety and efficacy requirements for approval, 21 C.F.R § 314.105(d), but must await expiration of an exclusivity granted to another party. 21 U.S.C. § 355(j)(5)(B)(iv)(II)(dd)(AA); 21 C.F.R. § 314.107(b)(3)(v)."); *AstraZeneca Pharms. LP v. Cobalt Pharms. Inc.*, Civil No. 10-0338, 2010 U.S. Dist. LEXIS 132727, at *14 (D. Del. Dec. 15, 2010) (same); *In re Wellbutrin SR Antitrust Litigation*, 749 F. Supp. 2d 260, 262 (E.D. Pa. 2010) (same).

[19] The FD&C Act describes certain events that can result in the forfeiture of a first applicant's 180-day generic drug exclusivity in section 505(j)(5)(D) of the FD&C Act. Among these is section 505(j)(5)(D)(i)(IV), which states that "[t]he first applicant fails to obtain tentative approval of the application within 30 months after the date on which the application is filed, unless the failure is caused by a change in or a review of the requirements for approval of the application imposed after the date on which the application is filed."

failure is caused by a change in or review of the *requirements for approval of the application*" (emphasis added) would be incongruous. Specifically, if an applicant is not required to satisfy the substantive requirements for approval in order to receive tentative approval, it would not make sense to provide that a change in the requirements for approval can be the basis for an exception to the requirement to secure a tentative approval within 30 months.

The fact that a tentative approval requires an applicant to meet all the substantive requirements for approval, including CGMP compliance, is reflected in the U.S. President's Emergency Plan for AIDS Relief (PEPFAR) program, which facilitates the availability of antiretroviral products to treat those infected with HIV/AIDS in other countries. Under this program, the U.S. Agency for International Development (USAID) allows products to be purchased for use abroad in the PEPFAR program if they have been tentatively approved by FDA. As FDA describes on its dedicated PEPFAR webpage:

> FDA reviews the marketing applications using its normal standards for authorization. If the product still has marketing protection in the U.S., FDA issues a "tentative approval" rather than a "full" approval. The "tentative" approval signifies that the product meets all safety, efficacy, *and manufacturing quality standards* for marketing in the U.S., and, but for the legal market protection, it would be on the U.S. market. USAID allows, under the President's Emergency Plan, purchase of any product that has either a "full" or "tentative" FDA approval. In this manner, the only products being offered under this program to the focus countries are products that we would offer our own citizens.[20]

In addition, FDA's Generic Drug User Fee Act (GDUFA) Commitment Letter reflects an agreement between FDA and the generic drug industry that in allocating its inspectional resources, FDA will prioritize "inspections of establishments associated with ANDAs that are otherwise approvable or eligible for tentative approval except for an outstanding inspection."[21] If such inspections were not required or permitted in connection with a tentative approval, there would be no reason to prioritize them over other inspections in this context. In other cases, FDA consistently has interpreted tentative approval such that outstanding compliance issues are an appropriate basis on which to withhold tentative approval of an ANDA. For example, FDA's September 25, 2014 approval of Ranbaxy's ANDA 091118 for certain strengths of minocycline

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[20] FDA Website: "Approved and Tentatively Approved Antiretrovirals in Association with the President's Emergency Plan," available at http://www.fda.gov/InternationalPrograms/FDABeyondOurBordersForeignOffices/AsiaandAfrica/ucm119231.htm (FDA PEPFAR Webpage) (Emphasis added.); see also guidance for industry on *Fixed Dose Combinations, Co-Packaged Drug Products, and Single-Entity Versions of Previously Approved Antiretrovirals for the Treatment of HIV* (Oct. 2006), available at http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm079742.pdf ("Products that receive a tentative approval undergo the same FDA review as products that are approved and marketed in the United States, and should meet the same safety, efficacy, and quality standards, including manufacturing and bioequivalence (BE) study inspections.")

[21] See, e.g., GDUFA Commitment Letter: Generic Drug User Fee Program Performance Goals and Procedures, at 8 (July 2012), available at http://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM282505.pdf.

hydrochloride extended-release tablets included a decision that Ranbaxy had forfeited 180-day exclusivity with respect to the 80 mg and 105 mg strengths.[22] This decision was based on FDA's determination that all substantive review disciplines were acceptable before the forfeiture deadlines for those strengths, and tentative approval was delayed only because of issues pertaining to the firm's compliance with FDA's CGMP regulations.[23]

B. 180-day Exclusivity and Exclusivity Forfeiture

An ANDA applicant also must include in its application one of the following certifications with respect to each patent for the listed drug the ANDA references:

(I) that such patent information has not been filed (a paragraph I certification),
(II) that such patent has expired (a paragraph II certification),
(III) of the date on which such patent will expire (a paragraph III certification), 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 (a paragraph IV certification).

Section 505(j)(2)(A)(vii) of the FD&C Act.[24] See also 21 CFR 314.94(a)(12)(i)(A).

An applicant submitting a paragraph IV certification to a listed patent must provide the NDA holder and the patent owner notice of its patent certification, including a description of the legal and factual basis for the ANDA holder's assertion that the patent is invalid or not infringed.[25] If the NDA holder or patent owner initiates a patent infringement action against the ANDA applicant before the expiration of 45 days after receiving the required notice, approval of the ANDA generally will be stayed for the 30 month period beginning on the date of receipt of the notice or such shorter or longer time as the court might order.[26]

The 180-day exclusivity provisions described in section 505(j)(5)(B)(iv) of the FD&C Act provide the first applicant(s)[27] to submit a paragraph IV certification challenging a patent — and thus to undertake the risk of litigation — an incentive in the form of the opportunity to be the only generic drug manufacturer(s) to compete with the innovator for a 180-day period. The

[22] Letter to S. Tomsky, Ranbaxy Labs. Ltd. fr. R. West, FDA Office of Generic Drugs re ANDA 091118, at 6 (Sept. 25, 2014).

[23] We note that FDA has applied this interpretation in the context of other ANDAs, but we are limited in disclosing the details of those decisions under FDA's disclosure regulations. 21 CFR 314.430.

[24] If a method of use patent for the reference listed drug does not claim a use for which the ANDA applicant seeks approval, the applicant must submit a statement that the method of use patent does not claim such a use. Section 505(j)(2)(A)(viii) of the FD&C Act; 21 CFR 314.94(a)(12)(i)(B)(iii)(A).

[25] Section 505(j)(2)(B) of the FD&C Act.

[26] Section 505(j)(5)(B)(iii) of the FD&C Act.

[27] A "first applicant" is "an applicant that, on the first day on which a substantially complete application containing a [paragraph IV certification] is submitted for approval of a drug, submits a substantially complete application that contains and lawfully maintains a [paragraph IV certification]." Section 505(j)(5)(B)(iv)(II)(bb) of the FD&C Act.

requirements for obtaining and retaining this 180-day exclusivity period are described at sections 505(j)(5)(B)(iv) and 505(j)(5)(D) of the FD&C Act.

The Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Pub. L. No. 108-173, 117 Stat. 2066 (MMA) (Dec. 8, 2003) describes, among other things, certain events that can result in the forfeiture of a first applicant's 180-day generic drug exclusivity as described in section 505(j)(5)(B)(iv) of the FD&C Act. Included among these is section 505(j)(5)(D)(i)(IV) of the FD&C Act, which states the following:

> FAILURE TO OBTAIN TENTATIVE APPROVAL.--The first applicant fails to obtain tentative approval of the application within 30 months after the date on which the application is filed, unless the failure is caused by a change in or a review of the requirements for approval of the application imposed after the date on which the application is filed.

The "failure to obtain tentative approval" forfeiture provision establishes a bright-line rule: If within 30 months after the date on which the application is submitted, an abbreviated new drug application (ANDA) has been determined by the agency to meet the statutory standards for approval and it is only patent and/or exclusivity protection that prevents full approval, then an applicant will be given a tentative approval and will maintain eligibility for 180-day exclusivity. If tentative approval is not obtained within 30 months, eligibility for 180-day exclusivity is generally forfeited unless "the failure [to obtain tentative approval] is caused by a change in or a review of the requirements for approval of the application imposed after the date on which the application is filed."

In addition, FDA has determined that if one of the causes of failure to obtain tentative approval by the 30-month forfeiture date was a change in or review of the requirements for approval imposed after the application was submitted, an applicant will not forfeit eligibility even if there may have been other causes for failure to obtain tentative approval by the 30-month forfeiture date.[28] Thus, to avoid forfeiture, an applicant must show that acceptability of at least one aspect of the ANDA (e.g., chemistry) was delayed, and that this delay was caused at least in part, by a change in or review of the requirements for approval, irrespective of what other elements may also have been outstanding at the 30-month date. In other words, "but-for" causation is not required to qualify for this exception. FDA has determined that this interpretation best effectuates the policy embodied in the exception. It does not penalize applicants for reviews of or changes in approval requirements imposed on applicants after their ANDAs are submitted that are a cause of the failure to obtain approvals or tentative approvals within 30 months (and presumes causation if, at the 30 month date, the applicant was actively addressing those changes), and continues to incentivize applicants to challenge patents by preserving, in many instances, the opportunity to obtain 180-day exclusivity.

[28] *Mylan Labs. Ltd. v. FDA*, 910 F. Supp. 2d 299, 302 (D.D.C. 2012).

II. FACTUAL BACKGROUND

A. Compliance History of Ranbaxy's Paonta Sahib Facility

FDA inspected Ranbaxy's Paonta Sahib, India facility from February 20-25, 2006. At the conclusion of that inspection, FDA investigators issued a Form FDA-483 documenting numerous significant deviations from CGMP in the manufacture of drug products, which included, but were not limited to:

a. Failure to include in laboratory records a complete record of all data secured in the course of each test, including all graphs, charts, and spectra from laboratory instrumentation, properly identified to show the specific drug product and lot tested, as required by 21 CFR 211.194(a)(4);
b. Failure to establish and follow an adequate written testing program designed to assess the stability characteristics of drug products and to determine appropriate drug storage conditions and expiration dates, as required by 21 CFR 211.166; and
c. Failure of the quality control unit to have adequate laboratory resources, including personnel and equipment, for conducting stability testing of drugs, as required by 21 CFR 211.22(b).

Ranbaxy submitted written responses dated March 20, April 20, and May 25, 2006, to the Form FDA-483 issued after the February 20-25, 2006 Paonta Sahib inspection. The responses stated that Ranbaxy took actions to restructure the stability group and institute a Management Review Committee to oversee the stability program. The responses adequately addressed some of the inspectional observations, but FDA continued to have concerns that: laboratory records did not include a complete record of all data secured in the course of each test, including all graphs, charts, and spectra from laboratory instrumentation, properly identified to show the specific drug product and lot tested; the firm failed to establish and follow an adequate written stability testing program designed to assess the stability characteristics of drug products and to determine appropriate storage conditions and expiration dates; and the Quality Control Unit lacked adequate laboratory resources (personnel and equipment) for conducting stability testing of drug products.

On June 15, 2006, FDA issued a Warning Letter stating that, based on the violations observed during FDA's February 20-25, 2006 inspection at the Paonta Sahib facility and taking into account Ranbaxy's March 20, April 20, and May 25, 2006 responses, the finished drug products manufactured at this facility were adulterated under section 501(a)(2)(B) of the FD&C Act because they were manufactured in violation of CGMP. This Warning Letter explained in detail FDA's above-cited concerns. The Warning Letter also stated that, "[u]ntil FDA has confirmed correction of the deficiencies observed during the most recent inspection and compliance with CGMP, this office will recommend withholding approval of any new applications listing your Paonta Sahib facility as the manufacturer of finished pharmaceutical drug products."

FDA inspected Ranbaxy's Paonta Sahib Batamandi (Unit II) facility from March 3-7, 2008. At the conclusion of that inspection, FDA investigators issued a Form FDA-483 documenting many

significant deviations from CGMP in the manufacture of finished drug products. These observations included, but were not limited to, the following:

a. Failure to keep written records of major equipment cleaning and use adequate to show that persons double-checked the performance of equipment cleaning, as required by 21 CFR 211.182;
b. Failure to include complete information in the batch production and control records prepared for each batch of drug product produced, as required by 21 CFR 211.188(b)(l1);
c. Failure to have adequate procedures for review and approval of drug product production and control records by the quality unit, including those for packaging and labeling, to determine compliance with all established, approved written procedures before a batch is released or distributed, as required by 21 CFR 211.192; and
d. Failure to extend investigations into any unexplained discrepancy or the failure of a batch or any of its components to meet any of its specifications to other batches of the same drug product and other drug products that may have been associated with the specific failure or discrepancy, whether or not the batch has already been distributed, as required by 21 CFR 211.192.

Ranbaxy submitted a written response dated May 1, 2008, to the Form FDA-483 issued after the March 3-7, 2008 Paonta Sahib Batamandi (Unit II) inspection. The response noted that some corrections had been implemented, including withdrawal of an ANDA due to deficiencies noted in equipment cleaning logs and batch production and control records for the exhibit batches of that drug manufactured in July - August, 2006. Ranbaxy's response did not adequately address FDA's concerns that the instances of discrepancies observed during the inspection were indications of continuing, systemic CGMP deficiencies at the Paonta Sahib facility.

On September 16, 2008, FDA issued a Warning Letter stating that, based on the violations observed during FDA's March 3-7, 2008 inspection at the Paonta Sahib Batamandi (Unit II) facility and taking into account Ranbaxy's May 1, 2008 response, the finished drugs manufactured at this facility were adulterated under section 501(a)(2)(B) of the FD&C Act because they were manufactured in violation of CGMP. This Warning Letter noted the continuing CGMP deficiencies in the quality systems at the Paonta Sahib facility, including the failure of production and quality management to prevent such deficiencies, and referenced the June 15, 2006 Warning Letter citing significant CGMP deficiencies relating to Paonta Sahib's stability testing program observed during FDA's February 20-25, 2006 inspection of that facility. The Warning Letter reiterated that "[u]ntil FDA has confirmed correction of the deficiencies and compliance with CGMP, this office will continue to recommend disapproval of any new applications listing the Paonta Sahib facility as the manufacturing location for finished pharmaceutical drug products."

B. Compliance History of Ranbaxy's Dewas Facility

FDA inspected Ranbaxy's Dewas, India facility from February 27 - March 2, 2006. At the conclusion of that inspection, FDA investigators issued a Form FDA-483 documenting deviations from CGMP including, but not limited to:

a. Failure to maintain complete data derived from all tests necessary to assure compliance with established specifications and standards, as required by 21 CFR 211.194;
b. Failure to have batch production and control records for each batch of drug product produced that includes complete information relating to the production and control of each batch, as required by 21 CFR 211.188; and
c. Failure to extend investigations into any unexplained discrepancy or the failure of a batch or any of its components to meet any of its specifications to other batches of the same drug product and other drug products that may have been associated with the specific failure or discrepancy, whether or not the batch has already been distributed, as required by 21 CFR 211.192.

FDA inspected the Dewas facility again from January 28 - February 12, 2008. At the conclusion of that inspection, FDA investigators issued a Form FDA-483 documenting significant deviations from CGMP in the manufacture of sterile and non-sterile finished products and in the manufacture and control of active pharmaceutical ingredients (APIs). These observations included, but were not limited to, the following:

a. Failure to adequately establish separate or defined areas for the manufacture and processing of non-penicillin beta-lactam products to prevent contamination and mixups, and failure to separate adequately the operations related to the manufacturing, processing, and packaging of penicillins from non-penicillin products, as required by 21 CFR 211.42(c)(5) and (d);
b. Failure to include required information relating to the production and control of each batch produced in batch production and control records, as required by 21 CFR 211.188(b);
c. Failure to have procedures that provide for a thorough review of unexplained discrepancies or failure of a batch or any of its components to meet its specifications, whether or not the batch has already been distributed, as required by 21 CFR 211.192;
d. Failure of the quality control unit to ensure that its organizational structure, procedures, processes, resources, and activities are adequate to ensure that APIs and drug products, sterile and non-sterile, meet their intended specifications for quality and purity, as required by 21 CFR 211.22;
e. Failure to have and follow adequate written procedures designed to prevent microbiological contamination of drug products and APIs purported to be sterile, as required by 21 CFR 211.113(b); and

f. Failure to have adequate controls established to prevent contamination or mix-ups in aseptic processing operations, as required by 21 CFR 211.42(c)(10).

Ranbaxy submitted a written response dated April 3, 2008, to the Form FDA-483 issued after the January 28 - February 12, 2008 Dewas inspection. The response noted that some corrections had been completed or would soon be implemented, but the response did not adequately address the multiple, serious deficiencies including the beta-lactam containment program and inadequacies in batch production and control records, failure investigations, quality control program, and aseptic operations.

On September 16, 2008, FDA issued a Warning Letter stating that, based on the violations observed during FDA's January 28 - February 12, 2008 inspection at Dewas and taking into account the firm's April 3, 2008 response, the sterile and non-sterile finished products and APIs manufactured at the facility were adulterated under section 501(a)(2)(B) of the FD&C Act because they were manufactured in violation of CGMP. The Warning Letter stated that "[u]ntil all corrections have been completed and FDA can confirm your firm's compliance with CGMP, this office will recommend disapproval of any new applications or supplements listing your firm as a manufacturing location of finished dosage forms and [APIs]."

C. Esomeprazole ANDA

Ranbaxy's ANDA 077830 for Esomeprazole Magnesium Delayed-release Capsules, 20 mg and 40 mg was received for review on August 5, 2005. Ranbaxy's ANDA was submitted on the first day on which a substantially complete ANDA containing a paragraph IV certification was received by the agency for these products. In its ANDA, Ranbaxy identified the company's Paonta Sahib facility as one of the facilities in which the company's Esomeprazole Magnesium Delayed-release Capsule products would be manufactured. By letter dated February 5, 2008, FDA informed Ranbaxy that ANDA 077830 was tentatively approved.[29]

At the time of FDA's February 5, 2008 letter, the Paonta Sahib facility had been the subject of a Warning Letter issued on June 15, 2006, based on the CGMP violations observed during FDA's February 20-25, 2006 inspection at the Paonta Sahib facility and taking into account Ranbaxy's March 20, April 20, and May 25, 2006 responses. Accordingly, at the time of the tentative approval letter, the compliance status of the Paonta Sahib facility was Official Action Indicated (OAI), which is an inspection conclusion reflecting that "objectionable conditions were found and a regulatory action is recommended."[30] Under such circumstances, Center for Drug Evaluation and Research Office of Compliance (CDER Compliance) will not recommend

[29] Letter to S. Tomsky, Ranbaxy Laboratories Limited fr. G. Buehler, Director, Office of Generic Drugs (Feb. 5, 2008).

[30] ORA-QMS FMD #86 (v.5.0): Establishment Inspection Report Conclusions and Decisions, at 16 (Jan. 28, 2014) (reflecting long-standing definition of OAI).

approval.[31] The overall compliance status for ANDA 077830 was "withhold," and the ANDA should not have been tentatively approved at that time due to the inspectional status.[32]

D. Valganciclovir ANDA

Ranbaxy's ANDA 078078 for Valganciclovir Hydrochloride Tablets USP, 450 mg, was received on December 27, 2005. It was the first substantially complete ANDA received by the agency for Valganciclovir Hydrochloride Tablets, 450 mg. Ranbaxy identified its Dewas facility as the drug substance manufacturer for Valganciclovir API and the Paonta Sahib facility as the finished dosage form manufacturer for its Valganciclovir Hydrochloride Tablet drug product. By letter dated June 20, 2008, FDA informed Ranbaxy that ANDA 078078 was tentatively approved.[33]

At the time of FDA's June 20, 2008 letter, the Dewas facility had been the subject of a January 28 - February 12, 2008 inspection that found significant deviations from CGMP in the manufacture of sterile and non-sterile finished products and in the manufacture and control of APIs, and that resulted in the issuance of a Warning Letter on September 16, 2008. The Paonta Sahib facility had been the subject of the Warning Letter issued on June 15, 2006, and the Paonta Sahib Batamandi (Unit II) facility had been the subject of a March 3-7, 2008 inspection that found many significant deviations from CGMP in the manufacture of finished drug products, and that resulted in the issuance of a Warning Letter on September 16, 2008. Accordingly, at the time of the tentative approval letter, the compliance status of the Dewas facility was "potential" OAI and the status of the Paonta Sahib facility was "OAI" and the ANDA should not have been tentatively approved at that time due to the inspectional status.

III. DISCUSSION

A. FDA Erred in Tentatively Approving Ranbaxy's ANDAs

Upon review of our records, the Agency has determined that FDA erred in tentatively approving Ranbaxy's ANDAs for Esomeprazole Magnesium Delayed-release Capsules, 20 mg and 40 mg, and Valganciclovir Hydrochloride Tablets, 450 mg. Specifically, the compliance status of the facilities referenced in the ANDAs at the time the ANDAs were granted tentative approval was inadequate to support approval or tentative approval, as described above. As explained above, FDA may not tentatively approve an ANDA like Ranbaxy's ANDAs for which there is evidence of non-compliance with CGMP. Accordingly, with this letter, the Agency is correcting its mistake and rescinding the tentative approval letters issued regarding these ANDAs. Additional correspondence providing information on the current status of each of these ANDAs as a result of this decision will be forthcoming.

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[31] FDA's Compliance Program Guidance Manual Program 7346.832 (New Drug Evaluation: Pre-Approval Inspections), Part V at 35 (Aug. 15, 1994) ("No application should be recommended for approval if the applicant is found in a state of non-compliance with the CGMP regulations that may adversely impact on the product(s) covered by the pending applications until satisfactory correction is made.")..

[32] OGD Approval Routing Summary for 077830 (Feb. 5, 2008).

[33] Letter to M. Yefimenko, Ranbaxy Inc. fr. G. Buehler, Director, Office of Generic Drugs (Jun. 20, 2008).

B. Forfeiture of Eligibility for 180-day Exclusivity for Valganciclovir Hydrochloride Tablets

With respect to your ANDA for Valganciclovir Hydrochloride Tablets USP, 450 mg, as noted above, Ranbaxy was the first ANDA applicant to submit a substantially complete ANDA with a paragraph IV certification. As a first applicant, Ranbaxy was eligible for 180 days of generic drug exclusivity. The Agency has determined, however, that Ranbaxy has forfeited its eligibility for 180-day exclusivity because Ranbaxy failed to obtain tentative approval of this ANDA within 30 months after the date on which the ANDAs were submitted. See section 505(j)(5)(D)(i)(IV) of the FD&C Act.

Specifically, at the 30-month forfeiture date for the Valganciclovir Hydrochloride Tablets ANDA, FDA determined that the chemistry, bioequivalence, and labeling sections of the ANDAs were acceptable.[34] As described in this letter, however, there was evidence of non-compliance with CGMP. The agency's conclusions with respect to the chemistry, bioequivalence, and labeling sections of the ANDA remain unchanged. The Agency finds, therefore, that even if there were a change in or review of the requirements for approval with respect to any of these aspects of the ANDA, these would have necessarily been satisfactorily resolved with respect to this application prior to the 30-month forfeiture date and could not have contributed to causing the failure of Ranbaxy to obtain tentative approval within 30-months. Therefore, the Agency finds that Ranbaxy's failure to obtain tentative approval within 30 months was not caused by a change in or review of the requirements for approval.

IV. CONCLUSION

For the reasons set forth above, FDA rescinds its previously granted tentative approval letters for Ranbaxy's ANDA for Esomeprazole Magnesium Delayed-release Capsules, 20 mg and 40 mg (ANDA 077830) and its ANDA for Valganciclovir Hydrochloride Tablets USP, 450 mg (ANDA 078078), and has determined that Ranbaxy has forfeited its eligibility for 180-day exclusivity for its ANDA for Valganciclovir Hydrochloride Tablets USP, 450 mg (ANDA 078078).

For further information on the status of these ANDAs, or prior to submitting additional amendments, please contact Heidi Lee, Project Manager for ANDA 077830 and/or Ryan Presto, Project Manager for ANDA 078078.

Sincerely yours,

{See appended electronic signature page}

Kathleen Uhl, M.D.
Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research

[34] OGD Approval Routing Summary for 078078 (Valganciclovir Hydrochloride Tablets), at 2.

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/s/

KATHLEEN UHL
11/04/2014