DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
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AUG 7 2013

Kumar Sekar, Ph.D.
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Bridgewater, NJ 08807-2862

Re: Docket No. FDA-2009-P-0266

Dear Dr. Sekar:

This letter responds to your petition submitted on behalf of Dr. Reddy's Laboratories, Inc. (Petitioner), which was received by the Food and Drug Administration (FDA or Agency) on June 10, 2009 (Petition). The Petition requests that FDA take the following action (Petition at 2-3):

1. Issue a Compliance Policy Guide (CPG) or guidance document establishing a procedure whereby a generic applicant can obtain a letter from FDA describing the Agency's findings that the applicant has agreed to applicable restrictions on distribution of the reference listed drug (RLD) necessary to assure safe use of the drug product during bioequivalence testing;
2. Incorporate into risk evaluation and mitigation strategies (REMS) that restrict product distribution, including those REMS currently under review for "deemed REMS" products, a provision stating that the RLD sponsor will not use REMS restricted distribution elements to assure safe use (ETASU) to delay or block generic competition;
3. Enforce the Federal Food, Drug, and Cosmetic Act (FD&C Act) against sponsors of RLDs subject to approved restricted distribution REMS including, to the extent possible, against those sponsors of "deemed REMS" products who have received a copy of a letter identified in number 1 above, but have nonetheless refused (explicitly or constructively) to sell, at fair market value, a sufficient quantity of the RLD to a proposed generic applicant for bioequivalence testing purposes; and
4. Refer to the Federal Trade Commission (FTC) any complaints received from generic drug manufacturers alleging that the sponsor of an RLD subject to an approved restricted distribution REMS has used such REMS in an anticompetitive manner to delay or block generic competition.

Although the Petition is specifically focused on generic applicants seeking approval of an abbreviated new drug application (ANDA) under section 505(j) of the FD&C Act,[1] the Petition suggests that these issues are also relevant to applicants seeking approval of an application submitted pursuant to section 505(b)(2) of the FD&C Act.

FDA has carefully considered your petition and other relevant information available to the Agency, including the comments to your petition submitted by Celgene Corporation (Celgene) on September 22, 2009. Based on our review of these materials and for the reasons described below, your petition is granted in part and denied in part.

I. BACKGROUND

The Petition concerns alleged anticompetitive practices undertaken by the sponsors of RLDs that are subject to REMS governing the drug's distribution through certain ETASU. Specifically, the Petition states that RLD sponsors may try to use these ETASU to block access to supplies of the RLD when needed for a potential generic competitor to conduct bioequivalence studies or otherwise satisfy the requirements for approval of a generic drug application (Petition at 1-3).

A. Statutory and Regulatory Basis for Approval of ANDAs Submitted Under Section 505(j) of the FD&C Act and NDAs Submitted Under Section 505(b)(2) of the FD&C Act

The Drug Price Competition and Patent Term Restoration Act of 1984 (Public Law 98-417) (the Hatch-Waxman Amendments) created sections 505(b)(2) and (j) of the FD&C Act. The Hatch-Waxman Amendments were intended to spur innovation with new incentives for drug development and to "make available more low cost drugs by establishing abbreviated approval processes."[2]

1. ANDAs

Section 505(j) of the FD&C Act established an abbreviated approval process for generic drugs. To obtain approval, an ANDA applicant is not required to provide independent evidence of safety and effectiveness, but instead may rely on the Agency's previous finding of safety and effectiveness for a drug that has been previously approved (the RLD). An ANDA applicant generally must show that its proposed product is bioequivalent to and

[1] 21 U.S.C. 355(j).

[2] See House Report No. 98-857, part 1, at 14-15 (1984), reprinted in 1984 U.S.C.C.A.N. 2647 at 2647-2648. Both ANDA and 505(b)(2) applicants are subject to applicable periods of marketing exclusivity and are required to submit an appropriate patent certification or statement for each patent that claims the listed drug or a method of using the drug for which the applicant is seeking approval and for which information is required to be filed under section 505(b)(1) or (c)(2) of the FD&C Act (see section 505(b)(2)(A)-(B) and (j)(2)(A)(vii)-(viii) of the FD&C Act).

has the same active ingredient, dosage form, route of administration, strength, labeling, and conditions of use as the RLD.[3]

The scientific premise underlying the Hatch-Waxman Amendments is that when certain aspects of drug products (e.g., active ingredient(s), strength, dosage form, and route of administration) are the same, the products are therapeutically equivalent, meaning that they can be expected to have the same clinical effect and safety profile, and therefore generally may be substituted for each other.

Drug products are therapeutic equivalents only if they are pharmaceutical equivalents and are bioequivalent.[4] "Pharmaceutically equivalent" drug products are those "in identical dosage forms that contain identical amounts of the identical active drug ingredient."[5] A generic drug product is bioequivalent to the RLD if "the rate and extent of absorption of the drug do not show a significant difference from the rate and extent of absorption of the RLD when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses."[6] The purpose of demonstrating bioequivalence to the RLD is to determine whether changes in the formulation affect the rate at or extent to which the active ingredient reaches the site of drug action.

2. *Section 505(b)(2) Applications*

A 505(b)(2) application is a new drug application (NDA) that relies for approval, at least in part, on data and information that are not owned by the applicant and to which the applicant does not have a right of reference. Although both 505(b)(2) applications and ANDAs may include comparisons to and reliance on the Agency's findings regarding an

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[3] See section 505(j)(2)(A) of the FD&C Act; see also 21 CFR 314.92(a) and 314.94(a). An applicant may submit an ANDA for a drug that has a different active ingredient, route of administration, dosage form, or strength from the RLD if the applicant has submitted a petition to the Agency (known as a *suitability petition*) requesting permission to file such an application and has received the Agency's approval (see sections 505(j)(2)(C) and (j)(4) of the FD&C Act; see also 21 CFR 314.93 and 314.127(a)). FDA will grant a suitability petition unless it determines that the safety and effectiveness of the proposed change from the listed drug cannot be adequately evaluated without data from investigations that exceed what may be required for an ANDA (see section 505(j)(2)(A) and (j)(2)(C) of the FD&C Act; see also 21 CFR 314.93(e)(1)(i)). Submission of an application under section 505(b) is required if investigations were necessary to evaluate the safety and effectiveness of the changed product; however, the 505(b)(2) pathway also may be used to seek approval for changes to an approved product that do not require additional investigations (see the draft guidance for industry on *Applications Covered by Section 505(b)(2)* (October 1999) (noting, with reference to the 1992 Final Rule, that "an applicant may submit a 505(b)(2) application for a change in a drug product that is eligible for consideration pursuant to a suitability petition under Section 505(j)(2)(C) of the [FD&C] Act")).

[4] *Approved Drug Products with Therapeutic Equivalence Evaluations* (Orange Book), Introduction at vi-vii.

[5] 21 CFR 320.1(c).

[6] Section 505(j)(8)(B)(i) of the FD&C Act; see also sections 505(j)(2)(A)(iv) and (j)(4)(F) of the FD&C Act and 21 CFR 314.94(a)(7) (requiring, as part of ANDA content and format, information to show that the drug product is bioequivalent to the RLD upon which the applicant relies), 314.127(a)(6)(i) (providing that FDA will refuse to approve an ANDA if information submitted is insufficient to show that the drug product is bioequivalent to the listed drug referred to in the ANDA), and 320.1(e)(defining *bioequivalence*).

RLD, as discussed above, with limited exceptions, an ANDA must contain evidence that the proposed drug is bioequivalent to the RLD and that the proposed drug labeling is the "same" as that of the approved listed drug. In contrast, a 505(b)(2) drug is not required to be bioequivalent to a listed drug or to have the same labeling as a listed drug.

A 505(b)(2) application, like an NDA submitted under 505(b)(1), must contain information adequate to show that the drug is safe and effective. The Agency may approve a 505(b)(2) application that relies on published literature or on the Agency's finding of safety and effectiveness for another listed drug product, provided that such reliance is scientifically justified. A 505(b)(2) applicant must also submit data necessary to support the safety and effectiveness of any aspects of the proposed drug product that represent modifications to or changes from the listed drug on which it relies.

3. Bioequivalence

The statute, regulations, and case law give FDA considerable flexibility in determining the appropriate method to establish bioequivalence.[7] Regardless of the methodology, with limited exceptions, bioequivalence studies involve the potential applicant obtaining supplies of the RLD in order to conduct the required comparisons.[8] Potential ANDA applicants therefore usually need to purchase supplies of the RLD product from a distributor of the drug or directly from the RLD sponsor. In some cases, the RLD sponsor has declined to provide potential ANDA applicants with access to the RLD product.

B. REMS

Title IX, Subtitle A, section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) amended the FD&C Act, adding new section 505-1(a), which authorizes FDA to require applicants to submit a proposed REMS as a part of an application if FDA determines that a REMS is necessary to ensure that the benefits of a drug outweigh its risks.[9] A REMS is a required risk management plan that uses elements, as specified in section 505-1 of the FD&C Act, beyond routine professional labeling (the package insert) to help ensure that the benefits of a drug outweigh its risks. Section 505-1(a) of the FD&C Act also authorizes FDA to require holders of covered applications approved without a REMS to submit a proposed REMS for the approved drug product if FDA becomes aware

[7] Under the regulations, "bioequivalence may be demonstrated by several in vivo and in vitro methods" (21 CFR 320.24(a)). In addition, FDA has the flexibility to use "[a]ny other approach deemed adequate by FDA to . . . establish bioequivalence" (21 CFR 320.24(b)(6)).

[8] An applicant is also required to retain a sample of both the test article and the RLD used to perform the studies (21 CFR 320.38 (retention of samples for bioavailability studies); 320.63 (retention of samples for bioequivalence studies)).

[9] Note that section 505-1 of the FD&C Act applies to applications for approval of prescription drugs submitted under sections 505(b) or (j) of the FD&C Act, as well as applications submitted under section 351 of the Public Health Service Act. These applications are termed *covered applications*, and refer to NDAs (including NDAs submitted under section 505(b)(2)), ANDAs, and biologics license applications (BLAs). The term *drug*, as used throughout this section of the response, is intended to refer to all products for which there are pending or approved *covered applications*.

of new safety information (as defined in section 505-1(b)(3)) and makes a determination that a REMS is necessary to ensure that the benefits of the drug outweigh its risks.

Further, section 909(b)(1) of FDAAA states that drugs approved prior to the effective date of FDAAA are "deemed to have in effect an approved risk evaluation and mitigation strategy under section 505-1 of the [FD&C Act]...if [there] are in effect on the effective date of [FDAAA] elements to assure safe use (A) required under [21 CFR 314.520 or 21 CFR 601.42]; or (B) otherwise agreed to by the applicant and [FDA]." Thus, persons with certain covered applications that were approved before the effective date of FDAAA were deemed to have in effect an approved REMS.[10]

A REMS may, if applicable criteria are met, include any or all of the following REMS elements: a medication guide (as provided for under 21 CFR part 208), a patient package insert (if such an insert may help mitigate a serious risk of the drug), a communication plan (if such a plan may support implementation of an element of the strategy), and/or ETASU.[11]

Section 505-1(f) of the FD&C Act specifies that ETASU may be required if a drug has been shown to be effective, but is associated with a serious adverse drug experience and can be approved only if (or would be withdrawn unless) such elements are required as part of a strategy to mitigate the specific serious risk(s) listed in the labeling of the product.[12] In addition, for a drug initially approved without ETASU, FDA must determine that other REMS elements (i.e., a Medication Guide or patient package insert, communication plan, and timetable for the submission of assessments) are not sufficient to mitigate the serious risks associated with the particular drug.[13]

ETASU must include one or more goals to mitigate the specific serious risk(s) listed in the drug's labeling,[14] and may include, among other things, requirements that health care providers who prescribe or administer the drug have particular training or are specially certified, that patients using the drug be monitored and/or enrolled in a registry, or that pharmacies, practitioners, or health care settings that dispense the drug be specially certified.[15]

Finally, section 505-1(f)(8) prohibits the holder of an approved application from using any ETASU required by FDA under section 505-1(f) to block or delay approval of an application under section 505(b)(2) or (j) of the Act. It is this provision that the Petitioner seeks to have FDA enforce through the steps requested in the Petition.

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[10] Such persons were also required, under section 909(b)(3) of FDAAA, to submit to FDA a proposed REMS not later than 180 days after the effective date of FDAAA.

[11] Sections 505-1(e) and (f) of the FD&C Act. A REMS for a drug approved under an NDA or BLA must also include a timetable for submission of assessments of the REMS (Section 505-1(d) of the FD&C Act).

[12] Section 505-1(f)(1)(A) of the FD&C Act.

[13] Section 505-1(f)(1)(B) of the FD&C Act.

[14] Section 505-1(f)(3) of the FD&C Act.

[15] Id.

II. DISCUSSION

A. Guidance Establishing a Procedure to Obtain a Letter Reflecting FDA's Findings Concerning the Adequacy of a Generic Applicant's Safeguards for the Use of a Drug for Bioequivalence Testing

The Petition requests that we issue a CPG or guidance document establishing procedures for a potential generic applicant to use to obtain a letter from FDA describing the Agency's finding that the potential applicant has agreed to take appropriate steps to assure safe use of a drug subject to a REMS with ETASU governing its distribution during bioequivalence testing (Petition at 2). FDA grants your request to the extent that the Agency intends to issue clarifying guidance on this topic.

When requested by potential generic applicants seeking to develop generic versions of drug products subject to REMS with ETASU governing product distribution, FDA has reviewed study protocols and related documents (e.g., informed consent forms) to ensure that they contain safety protections for study subjects comparable to those in the REMS for the RLD. Once FDA has determined that adequate safety protections are included in the protocol and related documents, FDA has sent the potential generic applicant correspondence describing this determination. Upon request by potential generic applicants who report difficulty obtaining samples of the RLD to complete necessary testing, FDA has also sent letters to specific RLD sponsors confirming the Agency's determination that the potential generic applicant's protocol includes necessary safety precautions comparable to those required by the REMS. These letters to RLD sponsors have also indicated that FDA will not consider it a violation of the REMS for the RLD sponsor to provide (or authorize the provision of) a sufficient quantity of the drug to allow the potential generic applicant to conduct testing necessary to support its ANDA.

In some cases, the Agency has requested revisions and resubmissions of protocols and related documents because the initial submissions were incomplete or inadequate. A guidance document clarifying both the procedure for requesting FDA review and the proper contents of protocol submissions could improve the quality of initial submissions and reduce associated review time. Accordingly, we grant your request for the issuance of guidance to the extent that FDA intends to issue a guidance document clarifying the procedures for and contents of such submissions.

B. Inclusion in REMS of a Provision Prohibiting Use of a REMS to Delay or Block Generic Competition

The Petition requests that FDA "[i]ncorporate into REMS that restrict product distribution…a provision stating that the listed drug sponsor will not use REMS restricted distribution elements to assure safe use to delay or block generic competition" (Petition at 2). For the reasons described below, we deny this request.

Section 505-1 of the FD&C Act authorizes FDA to require a REMS when a REMS is necessary to ensure that the benefits of a drug outweigh its risks, and the focus of a REMS is to mitigate the risks associated with a particular drug. Additionally, as described in detail

above, section 505-1 specifies the elements that may be included in a REMS, such as Medication Guides, communication plans, and ETASU. The prohibition in section 505-1(f)(8) on using ETASU to block or delay approval of an ANDA or (b)(2) application, which you have requested that FDA incorporate into REMS themselves, is not intended to ensure that the benefits of a drug outweigh its risks, and is not one of the safety-related elements enumerated in the FD&C Act that may be included in a REMS. Thus, FDA has not incorporated a provision prohibiting use of ETASU to block or delay generic competition into the contents of REMS themselves. We have, however, reminded sponsors of the prohibition in section 505-1(f)(8) via inclusion of the following language in REMS approval letters: "We remind you that section 505-1(f)(8) of the FD&C Act prohibits holders of an approved covered application with elements to assure safe use from using any element to block or delay approval of an application under section 505(b)(2) or (j). A violation of this provision in 505-1(f) could result in enforcement action."

For the reasons discussed above, your request that FDA include in the REMS themselves a provision stating that the RLD sponsor may not use ETASU to delay or block generic competition is denied.

C. Enforcement of the FD&C Act Against Sponsors of RLDs that Refuse to Sell a Sufficient Quantity of Their Drug Product to a Potential Generic Applicant for Bioequivalence Testing Purposes

The Petition requests that FDA enforce the FD&C Act against sponsors of RLDs subject to an approved restricted distribution REMS that refuse to sell a sufficient quantity of the drug to a potential generic applicant for bioequivalence testing purposes, despite receiving correspondence from FDA confirming that the prospective generic applicant's protocol includes necessary safety precautions comparable to those required by the REMS (Petition at 3).

Decisions with respect to initiating enforcement actions are generally made by the Agency on a case-by-case basis and are within the discretion of the Agency. Requests for the Agency to initiate enforcement actions are not within the scope of FDA's citizen petition procedures.[16] Accordingly, this request is denied.

D. Referral of Complaints to FTC

The Petition requests that FDA "refer to the FTC any complaints received from generic drug manufacturers alleging that the sponsor of a listed drug subject to an approved restricted distribution REMS has used such REMS in an anticompetitive manner to delay or block generic competition" (Petition at 3). The Agency agrees that issues related to ensuring that marketplace actions are fair and do not block competition would be best addressed by the FTC, which is the Federal entity most expert in investigating and addressing anticompetitive business practices. We have been in contact with the FTC regarding these issues and, when we receive complaints about these issues, we review them

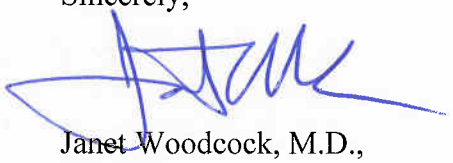
[16] See 21 CFR 10.30(k).

and refer them to FTC if appropriate. Insofar as FDA intends to refer complaints to FTC when appropriate, and to collaborate fully with the FTC in any investigation of such matters to the extent FDA can do so under its existing authority, this request is granted.

III. CONCLUSION

For the reasons set forth above, your petition is granted in part and denied in part.

Sincerely,



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