How to Obtain a Letter from FDA Stating that Bioequivalence Study Protocols Contain Safety Protections Comparable to Applicable REMS for RLD

Guidance for Industry

DRAFT GUIDANCE

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For questions regarding this draft document contact (CDER) Elizabeth Giaquinto 240-402-7930.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

December 2014
Generics

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http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

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This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This guidance describes how a prospective abbreviated new drug application (ANDA) applicant may request a letter stating that FDA has determined: (1) that the prospective applicant's bioequivalence (BE) study protocol contains safety protections comparable to those in the risk evaluation and mitigation strategy (REMS) with elements to assure safe use (ETASU) applicable to the reference listed drug (RLD), and (2) that FDA will not consider it a violation of the REMS for the RLD sponsor to provide a sufficient quantity of the RLD to the interested generic firm or its agent to allow the firm to perform the testing necessary to support its ANDA.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

A. ANDAs

The Drug Price Competition and Patent Term Restoration Act of 1984 (the Hatch-Waxman Amendments) created section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355(j)), which established the current ANDA approval process. To obtain approval to market a generic drug, an ANDA applicant is not required to submit clinical studies to establish the safety and effectiveness of the proposed generic drug product, but instead may rely

[1] This guidance has been prepared by the Office of Generic Drugs in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

on the Agency's previous finding of safety and effectiveness for the RLD. To do so, an ANDA applicant generally must demonstrate that its drug product is bioequivalent to, and has the same active ingredient, dosage form, route of administration, strength, labeling, and conditions of use as, the RLD (FD&C Act, section 505(j)(2)(A)).

BE is generally demonstrated via BE studies in which the proposed generic product is compared to the RLD. These studies require that the ANDA applicant has access to a sufficient quantity of the RLD to conduct the necessary comparisons between its test product and the RLD. Other testing (such as that necessary to establish the appropriate dissolution specifications for the proposed generic product) and/or regulatory requirements (such as those relating to the retention of reserve samples) may require the ANDA applicant to obtain additional supplies of the RLD.

B. REMS

Section 505-1(a)(1) of the FD&C Act authorizes FDA to require applicants to submit a proposed REMS as a part of the relevant application[2] if FDA determines that a REMS is necessary to ensure that the benefits of a drug outweigh its risks (21 U.S.C. 355-1(a)(1)). A REMS is a required risk management plan that uses tools beyond routine professional labeling (such as a medication guide, a patient package insert, and/or a communication plan) to ensure that the benefits of a drug outweigh its risks (FD&C Act, section 505-1(f)). In addition, FDA may require ETASU in some circumstances when such elements are necessary to mitigate the risks associated with the drug. ETASU may include, for example, requirements that health care providers who prescribe or administer the drug have particular training or certification, 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.

FDA is aware of instances in which an RLD sponsor has refused to sell drug product to a prospective ANDA applicant seeking to conduct the testing needed to obtain approval, and the RLD sponsor has cited the REMS ETASU as justification. In the interest of facilitating prospective generic applicants' access to RLD supplies to conduct the testing necessary to support ANDA approval, FDA has, on request, reviewed the BE study protocols proposed by prospective ANDA applicants to assess whether they provide safety protections comparable to those in the applicable REMS ETASU. When the Agency has determined that comparable protections existed, FDA has issued letters to the RLD sponsors stating so and indicating that FDA would not consider it to be a violation of the REMS for the RLD sponsor to provide drug product to the prospective ANDA applicant.

Requesting or obtaining such a letter from FDA is not a legal requirement. If a prospective ANDA applicant chooses to request such a letter, this guidance is intended to clarify the process for doing so.

[2] Section 505-1 of the FD&C Act applies to any application for approval of a prescription drug submitted under sections 505(b) or (j) of the FD&C Act (including both NDAs submitted under section 505(b)(2) and ANDAs submitted under section 505(j)), as well as applications submitted under section 351 of the Public Health Service Act (42 U.S.C. 262).

III. PROCEDURES FOR SUBMISSION AND REVIEW OF BIOEQUIVALENCE PROTOCOLS FOR DRUG PRODUCTS WITH REMS ETASU

A. Submission

- The prospective ANDA applicant should check the Agency's online listing of approved REMS[3] to determine whether the proposed RLD is subject to an approved REMS with ETASU. Study protocols for drugs not subject to approved REMS with ETASU should not be submitted to FDA for purposes of this guidance.

- If the proposed RLD is a drug product that is subject to an approved REMS with ETASU, the prospective ANDA applicant should prepare one or more (as necessary) complete BE protocol(s) that incorporate the elements of the RLD's labeling and ETASU that are necessary to conduct the BE study (or studies) in a safe manner. For example, if the applicable REMS is designed to prevent fetal exposure to a drug, then the BE protocol should protect against pregnancy in a manner comparable to what is provided for in the REMS.

- The prospective ANDA applicant may submit to GenericDrugs@fda.hhs.gov the draft BE protocol(s), all informed consent documents, and all informational materials that will be distributed to the study investigators, pharmacists, and subjects. Electronic submissions are strongly preferred.

B. FDA Review

- The Office of Generic Drugs' (OGD) Office of Bioequivalence's Division of Bioequivalence (DBE) and Division of Clinical Review (DCR) will review the draft BE protocol(s), informed consent document(s), and informational materials submitted. Others within the Agency may be consulted as necessary. Any concerns identified during this review will be communicated in a letter to the prospective ANDA applicant along with recommended changes.

- If there are recommended changes, the prospective ANDA applicant should revise the BE protocol(s), informed consent documents, and/or informational materials as appropriate and submit them to DBE and DCR for review. Electronic submissions are strongly preferred.

- If FDA determines that the protocols, informed consent documents, and informational materials contain safety protections comparable to those in the REMS ETASU, OGD will notify the prospective ANDA applicant in a letter that this determination has been made. This letter will advise the prospective ANDA applicant to provide a completed disclosure

[3] See Approved Risk Evaluation and Mitigation Strategies (REMS): www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm111350.htm.

authorization form (see Appendix) if they wish to have FDA issue a letter to the RLD sponsor, and will request that the prospective ANDA applicant provide FDA with the quantity of drug product per strength necessary to support its ANDA.

- At the prospective ANDA applicant's request, FDA will send a letter to the RLD sponsor stating that:
    - The Agency has determined that the protocols, informed consent documents, and informational materials contain safety protections comparable to those in the applicable REMS ETASU.
    - FDA will not consider it a violation of REMS for the RLD sponsor to provide the designated potential ANDA applicant (or its agent) a sufficient quantity of drug product to allow it to perform the testing necessary to support its ANDA and otherwise meet the requirements for ANDA approval.

APPENDIX

Dear [**insert name of Director, Office of Generic Drugs**]:

On behalf of **[insert name of prospective ANDA applicant]**, I authorize the United States Food and Drug Administration (FDA) to disclose the information described below to **[insert name of RLD holder]**. I understand that the information that is disclosed may contain confidential commercial or financial information or trade secrets within the meaning of 18 U.S.C. § 1905, 21 U.S.C. § 331(j), and 5 U.S.C. § 552(b)(4) that is exempt from public disclosure under those statutory provisions and/or relevant FDA regulations. I acknowledge that once this information is shared with **[insert name of RLD holder]**, it may not be subject to the same protections from disclosure that would otherwise be applicable. I agree to hold FDA harmless for any injury caused by FDA's sharing the information.

Information to be shared: FDA has received a request from **[insert name of prospective ANDA applicant]** for assistance in obtaining supplies of **[insert name of drug product]** for the purpose of testing a proposed generic **[active ingredient]** product against **[brand drug name]** as the reference listed drug. [**Insert name of prospective ANDA applicant]** has submitted for FDA's review study protocols that include safety precautions for testing comparable to those set forth in the FDA-mandated REMS for **[brand drug name]**.

Authorization is given to FDA to disclose the above-mentioned information which may include confidential commercial or financial information or trade secrets. As indicated by my signature, I am authorized to provide this consent on behalf of [**insert name of prospective ANDA applicant]** and my full name, title, address, telephone number, and facsimile number are set out below for verification.

Sincerely,

(Signature)

(Printed name)

(Title)

(Telephone & Facsimile Numbers)