

November 20, 2020

To,
Division of Dockets Management (HFA-305)
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852

WITHDRAWAL OF CITIZEN PETITION

Dear Sir / Madam,

The undersigned submits this request electronically under Section 505(j) of the Federal Food Drug, and Cosmetic Act and 21 CFR 10.30(g) for **Withdrawal of Citizen Petition ‘Docket No. FDA-2020-P-1792’** which was submitted to request FDA to designate suitable Approved Generic product as a Reference Standard (RS) for Metformin hydrochloride extended-release tablets 750 mg in FDA’s *Approved Drug Products with Therapeutic Equivalence Evaluations* (the Orange Book) upon which ANDA applicants can rely for purpose of comparative studies requirement.

A. Action Requested

Macleods Pharmaceuticals Limited requests the Food and Drug Administration (FDA) for withdrawal of Citizen Petition **‘Docket No. FDA-2020-P-1792’** as per 21 CFR 10.30(g)

B. Statement of Grounds

Macleods Pharmaceuticals Limited wish to withdraw Citizen Petition with allotted ‘Docket No. **FDA-2020-P-1792’** as the Citizen Petition request no longer holds valid due to following reasons;

1. Requirement of Controlled Correspondence for Designation of RLD:

As per Guidance for Industry, Referencing Approved Drug Products in ANDA Submissions, *Requesting Selection of a Reference Standard*, there are circumstances in which a potential ANDA applicant may ask FDA to select a reference standard. These circumstances include, for example, if FDA has not selected a reference standard, if a reference standard is moved to the Discontinued Section and FDA has not selected a new reference standard for the same drug product, if a potential ANDA applicant believes a reference standard other than the one selected by FDA is appropriate, or if the quantity of the reference standard in distribution is so limited that a potential ANDA applicant is not able to obtain a sufficient quantity for in vivo bioequivalence testing. A potential applicant may now submit controlled correspondence to FDA to ask FDA to select a reference standard for a drug product.

Hence, the Petitioner (Macleods) therefore respectfully requests FDA to consider the request for withdrawal of Citizen Petition 'Docket No. FDA-2020-P-1792'

In support of the above request, we have included the following data;

1. Guidance for Industry, Referencing Approved Drug Products in ANDA Submissions

C. Environmental Impact

The Petitioner claims a categorical exclusion from the requirement of an environmental assessment or environmental impact statement pursuant to 21 CFR § 25.31(a) and 25.15(d).

D. Economic Impact Statement

Information on the economic impact of the action requested by this Citizen Petition will be submitted if requested by FDA.

E. Certification

Macleods Pharmaceuticals Limited certifies, that to the best of knowledge and belief, this petition includes all information upon which this petition relies, and that it includes representative data and information known to the Petitioner which are unfavorable to this petition.

Sincerely,

Pooja Kulkarni,

GM, Regulatory Affairs

Macleods Pharmaceuticals Limited,

G-2, Mahakali Caves Road, Shanti Nagar,

Andheri (East), Mumbai - 400093, INDIA

Phone: + 91 22 61132900

Fax: + 91 22 28304641

e-mail : poojak@macleodspharma.com

Contact details of US agent

Mr. Andrej Gasperlin,

President, AB Pharmaceuticals, LLC

17471 Highland Way drive,

Chesterfield, MO 63005

Phone: (1) 314 814-2833

Fax: (1) 636 787-0604

e-mail : andrejg@macleodspharma.com



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring MD 20993

August 21, 2020

Pooja Kulkarni
General Manager, Regulatory Affairs
Macleods Pharmaceuticals Limited
G-2, Mahakali Caves Road, Shanti Nagar
Andheri (East), Mumbai – 400093, INDIA

Sent via email to: poojak@macleodspharma.com

Dear Petitioner:

Your petition to the Commissioner of Food and Drug Administration requesting the FDA designate a suitable reference standard for purpose of submitting an ANDA application for Metformin hydrochloride extended-release tablets 750 mg with reference to the current electronic orange book database was received by this office on 08/21/2020.

It was assigned docket number FDA-2020-P-1792. Please refer to this docket number in future correspondence on this subject with the Agency.

Please note that the acceptance of the petition for filing is a procedural matter and in no way reflects an agency decision on the substantive merits of the petition.

Sincerely,

Karen Malvin
Supervisory Administrative Proceedings Officer
Dockets Management Staff
FDA/Office of Operations (OO)

CC: Mr. Andrej Gasperlin (andrejg@macleodspharma.com)

Referencing Approved Drug Products in ANDA Submissions

Guidance for Industry

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

**October 2020
Generics**

Referencing Approved Drug Products in ANDA Submissions

Guidance for Industry

*Additional copies are available from:
Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research*

*Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993-0002*

Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353

Email: druginfo@fda.hhs.gov

<https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>

and/or

*Office of Communication, Outreach and Development
Center for Biologics Evaluation and Research
Food and Drug Administration*

*10903 New Hampshire Ave., Bldg. 71, Room 3128
Silver Spring, MD 20993-0002*

Phone: 800-835-4709 or 240-402-8010

Email: ocod@fda.hhs.gov

<https://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>

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

**October 2020
Generics**

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Referencing Approved Drug Products in ANDA Submissions Guidance for Industry¹

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA office responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance is intended to provide information to potential applicants on how to identify a reference listed drug (RLD), a reference standard, and the basis of submission in an abbreviated new drug application (ANDA) submission.²

Section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) permits any person to submit to the Food and Drug Administration (FDA or the Agency) an ANDA to seek approval to market a generic drug.³ FDA's regulations use certain terms for products that relate to an ANDA. In general, to obtain approval of an ANDA for a generic drug, an ANDA applicant first must identify the previously approved drug product it seeks to duplicate, i.e., the *reference listed drug (RLD)*, and must show, among other things, that the generic drug is bioequivalent to the RLD. A *reference standard*, which is selected by FDA, is the specific drug product that the ANDA applicant must use in conducting any in vivo bioequivalence testing required to support approval of its ANDA.⁴ The reference standard selected by FDA is ordinarily the RLD. However, there may be circumstances (e.g., when the RLD is no longer marketed) in which the reference standard is a drug product other than the RLD. In addition, FDA regulations require an ANDA applicant to include in an ANDA its "basis for ANDA submission" (referred to hereinafter as basis of submission).⁵ The basis of submission includes, among other things, the name of the RLD.

A variety of factors has led to confusion among stakeholders on what the terms RLD, reference standard, and basis of submission mean, and how ANDA applicants should use them. These factors include the discontinued marketing of many approved drug products and FDA's past practice of identifying reference standards with the RLD symbol ("+") in the printed version, and

¹ This guidance has been prepared by the Office of Generic Drugs in the Center for Drug Evaluation and Research at the Food and Drug Administration in cooperation with the Center for Biologics Evaluation and Research.

² An ANDA includes all amendments and supplements to the application. 21 CFR 314.3(b).

³ Throughout this guidance we use the term generic drug to refer to a new drug product described in an ANDA submitted under section 505(j) of the FD&C Act.

⁴ 21 CFR 314.3(b).

⁵ 21 CFR 314.94(a)(3).

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with a “Yes” under the “RLD” column in the electronic version, of FDA’s *Approved Drug Products with Therapeutic Equivalence Evaluations* (the Orange Book).⁶

The purpose of this guidance is to address this confusion by explaining what these terms mean and by clarifying the differences among them. This guidance provides recommendations on how applicants can accurately use these terms in an ANDA, how persons can request FDA designation of an RLD, and how persons can request FDA selection of a reference standard. Because of the confusion regarding use of these terms up until now, previously issued CDER guidances may not use these terms as we are clarifying them in this guidance.

In general, FDA’s guidance documents 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

The process for obtaining approval to market an innovator drug approved under a new drug application (NDA) differs from that for obtaining approval to market a generic drug under an ANDA. An NDA for an innovator drug must contain, among other things, a demonstration of the safety and effectiveness of the drug for the conditions of use for which approval is sought.⁷ A 505(b)(1) application, also known as a *stand-alone* NDA, is an application that contains full reports of investigations of safety and effectiveness that were conducted by or for the applicant or for which the applicant has a right of reference or use (referred to hereinafter as a 505(b)(1) NDA). A 505(b)(2) application is an NDA that contains full reports of investigations of safety and effectiveness where at least some of the information required for approval comes from studies not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use (e.g., published literature). An application submitted under section 505(b) is approved under section 505(c) of the FD&C Act.

To obtain approval for a generic drug, an ANDA applicant is not required to provide independent evidence of the safety and effectiveness of the proposed generic drug. Instead, the applicant relies on FDA’s finding that a previously approved drug product, i.e., the RLD, is safe and effective, and must demonstrate, among other things, that the proposed generic drug is the *same* as the RLD in certain ways. Specifically, with limited exceptions described in this section, a drug product for which an ANDA is submitted must have, among other things, the same active ingredient(s), conditions of use, route of administration, dosage form, strength, and (with certain permissible differences) labeling as the RLD.⁸ An ANDA applicant also must demonstrate that its proposed generic drug is bioequivalent to the RLD⁹ and, if in vivo bioequivalence studies are

⁶ The Orange Book is available at <http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm>.

⁷ Section 505(b)(1) of the FD&C Act.

⁸ Section 505(j)(2)(A), (j)(2)(C), and (j)(4) of the FD&C Act; see also 21 CFR 314.94(a).

⁹ Section 505(j)(2)(A)(iv) of the FD&C Act.

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required for approval of the ANDA, the applicant must use the reference standard selected by FDA.¹⁰ A generic drug must meet the same high standards of quality and manufacturing as drug products approved under section 505(c) of the FD&C Act.¹¹

FDA's approval of an ANDA for a generic drug that is a duplicate¹² of an RLD reflects the Agency's determination that the proposed generic drug is therapeutically equivalent to its RLD. Therapeutic equivalents are approved drug products that are pharmaceutical equivalents for which bioequivalence has been demonstrated, and that can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling.¹³

To submit an ANDA for a generic drug that is not the *same* as its RLD because it has one different active ingredient (in a fixed combination drug product), or has a different route of administration, dosage form, or strength than that of the RLD, an applicant first must obtain permission from FDA through the citizen petition process.¹⁴ Such petitions are referred to as *suitability petitions*. FDA will not approve a suitability petition if, for instance, investigations must be conducted to show the safety and effectiveness of the proposed generic drug.¹⁵ Because therapeutic equivalents must be pharmaceutical equivalents¹⁶, a generic drug for which FDA permits a difference under an approved suitability petition (petitioned ANDA) is not therapeutically equivalent to its RLD.

III. DISCUSSION

A. Listed Drug

FDA regulations define a *listed drug* as

a new drug product that has been approved under section 505(c) of the [FD&C Act] for safety and effectiveness or under section 505(j) of the [FD&C Act], which has not been withdrawn or suspended under section 505(e)(1) through (5) or section (j)(6) of the [FD&C Act], and which has not been withdrawn from sale for what FDA has determined are reasons of safety or effectiveness.¹⁷

¹⁰ See 21 CFR 314.3(b).

¹¹ Section 505(j)(2)(A)(vi) of the FD&C Act.

¹² The term *duplicate* generally refers to a "drug product that has the same active ingredient(s), dosage form, strength, route of administration, and conditions of use as a listed drug." See 54 FR 28872 at 28877 (July 10, 1989). However, the term *duplicate*, as used in this context, does not mean identical in all aspects to the listed drug.

¹³ See 21 CFR 314.3(b). Pharmaceutical equivalents are drug products in identical dosage forms and route(s) of administration that contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified-release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; do not necessarily contain the same inactive ingredients; and meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. See 21 CFR 314.3(b).

¹⁴ Section 505(j)(2)(C) of the FD&C Act; 21 CFR 314.93(b).

¹⁵ 21 CFR 314.93(e)(1)(i).

¹⁶ See 21 CFR 314.3(b).

¹⁷ 21 CFR 314.3(b); see also section 505(j)(7) of the FD&C Act.

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Drug products approved under an NDA, either a 505(b)(1) or a 505(b)(2) application, may be listed drugs. Likewise, a drug product approved under an ANDA may be a listed drug. A drug product is deemed to be a listed drug on the date of approval of the NDA or ANDA for the drug product.¹⁸ Each strength of a drug is a distinct drug product and, therefore, a distinct listed drug. Listed drugs appear in FDA's Orange Book.

When a drug product is approved, generally it appears in the Orange Book section entitled the "Prescription Drug Product List" or the "Over-the-Counter Drug Product List"; these sections are commonly referred to as the *Active Section*. When an approved drug product is not marketed, it appears in the Orange Book's "Discontinued Drug Product List," which is commonly referred to as the *Discontinued Section*. In general, a listed drug is moved to the Discontinued Section when the applicant notifies FDA that it is withdrawing the listed drug from sale or the listed drug is not available for sale or FDA otherwise determines that the listed drug has been withdrawn from sale or is not available for sale.¹⁹ A listed drug also may be moved to the Discontinued Section if the applicant requests that approval of the NDA or ANDA be withdrawn because the drug product is no longer being marketed.²⁰

B. Reference Listed Drug

1. FDA's Identification of Listed Drugs That Have Been Designated as RLDs

The FD&C Act and FDA's regulations require an ANDA applicant to "refer" in its ANDA to the specific listed drug on which the applicant relies in seeking approval of its ANDA.²¹ This listed drug is the RLD.²²

Because an ANDA applicant is relying on FDA's finding that the RLD is safe and effective, FDA's general practice is to designate as RLDs drug products that have been approved for safety and effectiveness under section 505(c) of the FD&C Act. Although drug products that were submitted and approved under section 505(j) of the FD&C Act, which was established by the *Drug Price Competition and Patent Term Restoration Act of 1984* (Public Law 98-417), commonly referred to as the Hatch-Waxman Amendments, are listed drugs and may be selected as reference standards, FDA generally does not intend to designate these products as RLDs.

¹⁸ 21 CFR 314.3(b).

¹⁹ Section 506I of the FD&C Act requires the holder of an application approved under section 505(c) or (j) of the FD&C Act to submit certain notifications to FDA regarding the marketing status of the drug product, and requires FDA to update the Orange Book based on the information provided. For more information see FDA's draft guidance for industry *Marketing Status Notifications Under Section 506I of the Federal Food, Drug, and Cosmetic Act* (January 2019). When final, this guidance will represent FDA's current thinking on this topic.

²⁰ An applicant may request that approval of an NDA or ANDA be withdrawn because the drug product that is the subject of the NDA or ANDA is no longer being marketed. 21 CFR 314.150(c). FDA will withdraw approval of the NDA or ANDA based on the applicant's request provided none of the conditions in 314.150(a) or (b) applies.

²¹ Section 505(j)(2) of the FD&C Act; 21 CFR 314.94(a)(3).

²² 21 CFR 314.3(b). There may be multiple approved drugs each of which may be eligible to be an RLD for a particular drug product (e.g., either Trandate 100 milligram (mg) tablets (NDA 018716) or Normodyne 100 mg tablets (NDA 018687) are eligible to be the RLD for an ANDA for Labetalol Hydrochloride 100 mg tablets).

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FDA identifies in the Orange Book listed drugs that have been designated as RLDs. A listed drug approved for safety and effectiveness under section 505(c) of the FD&C Act that appears in the Active Section of the Orange Book may be eligible to be an RLD. A listed drug approved for safety and effectiveness under section 505(c) of the FD&C Act that appears in the Discontinued Section also may be eligible to be an RLD, unless FDA makes a determination that the listed drug was withdrawn from sale for reasons of safety or effectiveness. If FDA makes such a determination, the listed drug will be removed from the Orange Book and is no longer eligible to be an RLD.²³

Under FDA regulations, the Agency may determine at any time whether a listed drug was withdrawn from sale for reasons of safety or effectiveness. However, FDA must determine whether a listed drug was withdrawn from sale for reasons of safety or effectiveness: (1) before FDA can approve an ANDA that refers to the listed drug as its RLD; (2) whenever the listed drug is voluntarily withdrawn from sale if any approved ANDA already refers to that listed drug; and (3) when any person petitions for such a determination.²⁴ These determinations are completed by the Agency and subsequently are published in a Notice in the Federal Register.²⁵ Historically FDA generally did not approve ANDAs for which the Agency had made a determination that the RLD was not withdrawn from sale for reasons of safety or effectiveness until after that determination was published in a Notice in the Federal Register. In order to expedite the availability of generic drugs, FDA decided that it may approve a generic drug for which it has made a final determination that the RLD was not withdrawn from sale for safety or effectiveness reasons even if that determination has not yet published in a Notice in the Federal Register and will proceed with Federal Register publication as expeditiously as is practicable.

If FDA determines that a listed drug in the Discontinued Section was not withdrawn from sale for safety or effectiveness reasons and publishes that determination in a Notice in the Federal Register, the Agency generally adds the following notation to that product listing information in the Orange Book: “**Federal Register determination that product was not discontinued or withdrawn for safety or efficacy reasons**.”²⁶ If FDA determines that the listed drug was withdrawn from sale for reasons of safety or effectiveness, the Agency will remove the listed drug from the Orange Book and the Agency will not accept for review or approve ANDAs that refer to the drug product.²⁷

2. Choosing an RLD

²³ 21 CFR 314.162.

²⁴ 21 CFR 314.161(a).

²⁵ See, e.g., Determination that KENALOG (Triamcinolone Acetonide) Lotion and Other Drug Products Were Not Withdrawn From Sale for Reasons of Safety or Effectiveness (81 FR 13797; March 15, 2016); and Determination that Ondansetron (Ondansetron Hydrochloride) Injection, USP, in PL 2408 Plastic Container, 32 Milligrams in 50 Milliliters, Was Withdrawn From Sale for Reasons of Safety or Effectiveness (80 FR 32962; June 10, 2015).

²⁶ The Orange Book may not include notations for all such determinations published in Notices in the Federal Register and does not reflect determinations published in Notices in the Federal Register before 1995. A potential applicant should refer to the Federal Register to see if FDA has published a Notice that announces a determination about whether a listed drug has been voluntarily withdrawn from sale for safety or effectiveness reasons.

²⁷ 21 CFR 314.162(a).

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An ANDA applicant must first choose an RLD. If FDA has not designated an RLD for a drug product the applicant intends to duplicate, the potential applicant may submit controlled correspondence to FDA identifying the drug it intends to duplicate (e.g., by NDA number and by active ingredient, dosage form, route of administration and strength) and asking FDA to designate an RLD.²⁸

If FDA has designated a listed drug as an RLD, but the potential applicant intends to refer to a different listed drug that was approved for safety and effectiveness under section 505(c) of the FD&C Act and is a pharmaceutical equivalent to the drug designated as an RLD, the potential applicant may submit controlled correspondence to FDA to request that FDA designate that different listed drug as an RLD.

For an ANDA based on an approved suitability petition (a *petitioned ANDA*), an applicant must choose as its RLD the listed drug that is referenced in the approved suitability petition.²⁹

If an RLD appears in the Discontinued Section and FDA has not published in the Federal Register a determination whether the drug was withdrawn from sale for reasons of safety or effectiveness, the applicant must submit a citizen petition seeking a safety and effectiveness determination for the listed drug at the same time as the ANDA submission.³⁰ Such petition must contain all evidence available to the petitioner concerning the reason that the drug product was withdrawn from sale.³¹ A determination whether an RLD has been withdrawn for safety or effectiveness reasons must be made before FDA may approve an ANDA that refers to an RLD in the Discontinued Section.³²

If an applicant has a question about which listed drug it should identify as the RLD, the applicant may submit controlled correspondence to seek input from the Agency.

3. The Role of an RLD in an ANDA

The RLD is the listed drug to which the ANDA applicant must show its proposed generic drug is the same with respect to active ingredient(s), dosage form, route of administration, strength, labeling, and conditions of use, among other characteristics.

²⁸ See FDA's draft guidance for industry on *Controlled Correspondence Related to Generic Drug Development* (November 2017). When final, this guidance will represent FDA's current thinking on this topic. We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

²⁹ 21 CFR 314.94(a)(3)(i).

³⁰ 21 CFR 314.122(a). If a citizen petition seeking a safety and effectiveness determination for the listed drug already has been submitted to FDA, the ANDA applicant should reference the pending petition in its ANDA and FDA will consider the ANDA to "be accompanied by" the petition. *Id.* If the listed drug is moved to the Discontinued Section while the ANDA is pending, a safety and effectiveness determination must be made by FDA before the ANDA can be approved. 21 CFR 314.161(a)(1).

³¹ 21 CFR 314.122(a). FDA will consider the evidence in the petition, as well as any other information before the Agency, to determine whether the listed drug was withdrawn from sale for safety or effectiveness reasons. 21 CFR 314.122(b).

³² 21 CFR 314.161(a).

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Regarding the *same labeling* requirement, the generic drug must have the same labeling as the RLD, except for differences permitted under the FD&C Act and Agency regulations.³³ Accordingly, an ANDA applicant must compare its proposed product's labeling to that of the RLD, even if FDA has selected a new *reference standard* for use in in vivo bioequivalence studies, as described in detail in section III.C. below.³⁴ Similarly, in evaluating drug product formulation and inactive ingredients, an ANDA applicant must compare its proposed generic drug to the RLD's formulation, not the formulation of the reference standard.

4. Identification of the RLD in the Orange Book

Prior to 2017, the column in the electronic Orange Book labeled "RLD," and the symbol in the printed version described as identifying the RLD, at times indicated the drug product FDA selected as the reference standard and at other times indicated the RLD, contributing to confusion about which drug is the RLD and which drug is the reference standard. In 2017, FDA began to identify in the Orange Book which listed drugs, including some in the Discontinued Section, FDA has designated as RLDs, and which listed drugs in the Active Section FDA has selected as reference standards. In the electronic Orange Book, there is a column for RLDs and a column for reference standards. In the printed version of the Orange Book, the RLDs and reference standards are identified by distinct symbols.

5. Changing the RLD

Once an ANDA applicant chooses the RLD on which it intends to rely, the FD&C Act and FDA regulations prohibit the applicant from amending or supplementing its ANDA to change the RLD after the ANDA has been submitted.³⁵ An ANDA applicant that seeks to change its RLD

³³ The FD&C Act and FDA's regulations permit labeling differences because of differences approved under a suitability petition or because the generic drug and the RLD are produced or distributed by different manufacturers. Section 505(j)(4)(G) of the FD&C Act and 21 CFR 314.94(a)(8)(iv). In certain instances, the labeling for the generic drug may differ from the labeling for the RLD if FDA permits the ANDA applicant to omit (*carve out*) an indication or other aspect of the RLD's labeling protected by patent, or by exclusivity, and obtain approval for the remaining, non-protected conditions of use, provided the differences do not render the proposed product less safe or effective than the RLD for all remaining non-protected conditions of use. See, e.g., section 505(j)(2)(A)(viii) of the FD&C Act; 21 CFR 314.127(a)(7).

³⁴ An applicant is responsible for checking appropriate sources in order to obtain the RLD labeling. FDA posts approved labels and labeling for most drug products on Drugs@FDA (<http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm>). Other sources such as FDA's Online Label Repository at <https://dailymed.nlm.nih.gov/dailymed/index.cfm>, and PRPLLR™ (Pragmatic Regulated Product Labeling Listing and Registration) may not necessarily display the most recently approved labeling. In instances where the RLD labeling cannot be located, an applicant for convenience initially may compare its proposed generic drug's labeling with the labeling of another ANDA that referenced the same RLD and currently is marketed. Where FDA has withdrawn approval of the application for the RLD for reasons other than safety or effectiveness, the ANDA applicant, before approval of the generic drug, may need to revise labeling to reflect certain updated information that would have been necessary for the RLD had the application for the RLD not been withdrawn. See FDA's draft guidance for industry *Updating ANDA Labeling After the Marketing Application for the Reference Listed Drug Has Been Withdrawn* (July 2016). When final, this guidance will represent FDA's current thinking on this topic.

³⁵ Section 505(j)(2)(D) of the FD&C Act; 21 CFR 314.96(c) and 314.97(b). We note that where an applicant has previously mistakenly identified the reference standard (described in detail in section III.C.) as the RLD on Form

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must submit a new ANDA to obtain approval under section 505(j) of the FD&C Act.³⁶ We recommend that an ANDA applicant request withdrawal of the pending ANDA before seeking to change its RLD.

C. Reference Standard

1. Selection of a Reference Standard

As discussed above, the FD&C Act requires an ANDA to provide “information to show that the new drug is bioequivalent” to its RLD.³⁷ If bioequivalence is not self-evident, there are a variety of methods by which bioequivalence may be demonstrated, including in vivo studies (in human subjects), in vitro studies (conducted in a laboratory), or both.³⁸

A “reference standard” is the drug product selected by FDA that an applicant seeking approval of an ANDA must use in conducting an in vivo bioequivalence study required for approval of the ANDA.³⁹ FDA generally selects a single reference standard to ensure the greatest level of consistency between a generic drug and its RLD and among generic drugs. Ordinarily, FDA selects the RLD as the reference standard.⁴⁰ FDA usually selects as the reference standard the highest strength available for drug products with multiple approved strengths.⁴¹

If drug products are approved for multiple strengths but FDA has selected only one of the strengths as the reference standard, an applicant may use other approved strengths for certain testing, other than in vivo bioequivalence testing (e.g., dissolution testing to support approval of those strengths not selected as the reference standard), if the use of such drug product in the particular testing is scientifically supported.

FDA 356h or elsewhere in its ANDA, the applicant may submit an amendment to a pending ANDA or a supplement to an approved ANDA to *correct* the information. FDA considers this error to be a deficiency related to identification of the appropriate listed drug as the RLD, rather than a change in the RLD itself. The cover letter for such a submission should clearly identify that the purpose of the submission is “Correction of RLD information.”

³⁶ Section 505(j)(2)(D)(i) of the FD&C Act; 21 CFR 314.96(c) and 314.97(b). But see section 505(j)(2)(D)(ii) of the FD&C Act.

³⁷ Section 505(j)(2)(A)(iv) of the FD&C Act.

³⁸ 21 CFR 320.24.

³⁹ 21 CFR 314.3(b). We note that in vivo bioequivalence evidence is not required in all circumstances, see, e.g., 21 CFR 320.22 and 320.24(b)(6). When in vivo bioequivalence testing is required or an applicant otherwise seeks to support a demonstration of bioequivalence with in vivo data, such testing should be conducted with the drug product FDA selects as the reference standard. Although the regulations do not require that an applicant use a particular product for in vitro testing, we recommend that the reference standard also be used for in vitro testing.

⁴⁰ An ANDA applicant may use the authorized generic version of the reference standard for purposes of conducting an in vivo bioequivalence study required for approval. See section 505(t) of the FD&C Act for additional information on authorized generics. The ANDA applicant may contact the Office of Generic Drugs via controlled correspondence before conducting studies to inquire further and to discuss the necessary documentation.

⁴¹ See *Abbreviated New Drug Applications and 505(b)(2) Applications; Final Rule*, 81 FR 69580 at 69619 (October 6, 2016). There may be instances in which the highest strength would not be the appropriate reference standard for testing in vivo bioequivalence or the highest strength is not available for testing. For example, FDA may select a different strength if testing at a different strength provides greater assurance of safety for the subject or is more feasible in terms of recruiting subjects who meet the study criteria. FDA also may, in limited circumstances, select multiple strengths in a single application as reference standards, e.g., if there is disproportionality among the product strengths.

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Where FDA cannot select the RLD as the reference standard (e.g., where the RLD has been withdrawn from sale for reasons other than safety and effectiveness), FDA generally will select a previously approved ANDA that referred to, and is therapeutically equivalent to, the RLD as the reference standard. If there are multiple approved generic drugs that referred to the RLD and have the same active ingredient, dosage form, route of administration, and strength, FDA usually will select the generic market leader, based on commercial data, as the reference standard. Where a generic drug is intended to duplicate a drug product approved in a petitioned ANDA, FDA generally selects a generic drug product approved under the petitioned ANDA as the reference standard.

As discussed above, even if FDA selects a reference standard that is a drug product other than the RLD for use in conducting in vivo bioequivalence studies, an ANDA applicant must demonstrate that its proposed generic drug meets the sameness requirements in section 505(j) of the FD&C Act and Agency regulations in relation to the RLD.

Before 2017, a reference standard selected by FDA was indicated in the electronic version of the Orange Book with the word “Yes” in the “RLD” column, and in the paper version of the Orange Book with the “+” symbol, for drug products listed in the Active Section. In 2017, FDA modified the Orange Book to clarify which listed drugs are reference standards. In the Active Section of the electronic Orange Book, there is a column for RLDs and a column for reference standards. In the Active Section of the printed version of the Orange Book, the RLDs and reference standards are identified by distinct symbols.

2. Selection of a New Reference Standard

FDA may select a new reference standard when doing so will help to ensure that applications for generic drugs may be submitted and evaluated. In making a decision whether to select a new reference standard, FDA may consider, among other factors:

- Whether the listed drug that is the reference standard is no longer marketed
- Whether selecting a new reference standard would help to prevent a shortage of a particular drug product or category of drug products;⁴²
- Whether or not the current reference standard is also the RLD, and the Agency determines that the quantity of the current reference standard in distribution is so limited that a potential ANDA applicant is not able to obtain a sufficient quantity for in vivo

⁴² Executive Order 13588 on reducing prescription drug shortages was issued on October 21, 2011, and directs FDA to take steps to help prevent and reduce current and future disruptions in the supply of lifesaving drug products. For example, in June 2013, FDA removed Doxil (NDA 050718) as the reference standard for doxorubicin hydrochloride (HCl) liposome injection and selected Lipodox (ANDA 203263) as the reference standard. The shortage and continued unavailability of Doxil, a lifesaving drug product for cancer treatment, meant that there existed no available reference standard against which to test a generic doxorubicin HCl liposome injection product, effectively blocking generic competition to Doxil.

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bioequivalence testing (even if the current reference standard has not been withdrawn from sale).

When selecting a new reference standard, FDA generally selects a drug product that is therapeutically equivalent to the RLD and is the market leader based on commercial data. In certain circumstances, FDA will consider additional factors in selecting a new reference standard. For example, as a practical matter, FDA may consider whether potential reference standards are approved under applications that cover all the RLD strengths, which may make the development process more efficient, or whether a potential reference standard is approved for the particular strength that is recommended by FDA for use in in vivo bioequivalence studies in a product-specific guidance.⁴³

3. Requesting Selection of a Reference Standard

There are circumstances in which a potential ANDA applicant may ask FDA to select a reference standard. These circumstances include, for example, if FDA has not selected a reference standard, if a reference standard is moved to the Discontinued Section and FDA has not selected a new reference standard for the same drug product, if a potential ANDA applicant believes a reference standard other than the one selected by FDA is appropriate, or if the quantity of the reference standard in distribution is so limited that a potential ANDA applicant is not able to obtain a sufficient quantity for in vivo bioequivalence testing. A potential applicant may submit controlled correspondence to FDA to ask FDA to select a reference standard for a drug product. If the Agency selects a new reference standard, that product generally will remain the reference standard even if the original reference standard resumes marketing.

Some stakeholders refer to some generic drugs that are reference standards as *second RLDs*.⁴⁴ That description is not accurate and has generated confusion regarding generic drug development and the role of the reference standard relative to that of the RLD for both industry and the Agency. For example, FDA has received citizen petitions requesting designation of a second RLD, when in fact the petition is requesting that FDA select a new reference standard. In addition, ANDA applicants mistakenly have compared their proposed generic drugs to a reference standard to meet requirements for approval other than in vivo bioequivalence. While the reference standard is selected by FDA for the purpose of conducting any in vivo bioequivalence studies required for approval, an ANDA applicant must demonstrate that its proposed generic drug meets the sameness requirements in section 505(j) of the FD&C Act and Agency regulations in relation to the RLD. Accordingly, an ANDA's proposed labeling and formulation must be compared to the RLD, and not the reference standard, and the applicant must address any unexpired patents and exclusivity for the RLD as required.⁴⁵

D. Basis of Submission

An ANDA applicant must identify in its application the basis of submission.⁴⁶

⁴³ See generally, guidance for industry *Bioequivalence Recommendations for Specific Products* (June 2010).

⁴⁴ See the discussion in section III.B.1 of this guidance.

⁴⁵ See, e.g., section 505(j)(2)(B) of the FD&C Act; 21 CFR 314.94(a)(12).

⁴⁶ 21 CFR 314.94(a)(3).

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1. Basis of Submission for an ANDA for a Generic Drug That Is a Duplicate of Its RLD

When an applicant submits an ANDA for a generic drug that is a duplicate of its RLD, i.e., not a petitioned ANDA, the basis of submission is the RLD. Accordingly, the name of the RLD, including dosage form and strength, and its application number⁴⁷ should be provided as the basis of submission on Form FDA 356h (i.e., the form that accompanies regulatory submissions by an applicant) and in the appropriate sections of the ANDA. If the reference standard selected by FDA for the drug product is not the RLD, an applicant should **not** identify the reference standard as the basis of submission on Form FDA 356h. However, the reference standard should be identified in the relevant sections of the ANDA that include information pertaining to bioequivalence, such as 1.12.11 Basis for submission statement (which statement provides information about the proposed generic drug broadly, including bioequivalence and other information), 2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods, 5.2 Tabular listing of all clinical studies, and 5.3.1 Reports of biopharmaceutic studies.⁴⁸ FDA guidance and technical documents related to ANDA formatting are maintained and updated on FDA's website.⁴⁹

2. Basis of Submission for a First Petitioned ANDA

When an applicant submits a petitioned ANDA,⁵⁰ the basis of submission is the RLD and the approved suitability petition. The ANDA must contain: (1) the name of the RLD, which must be the same as the listed drug identified in the approved suitability petition; (2) a reference to the suitability petition's FDA-assigned docket number; and (3) a copy of FDA's correspondence approving the suitability petition.⁵¹ An applicant should identify on Form FDA 356h both the RLD and the RLD's application number, just as it would on Form FDA 356h for a non-petitioned ANDA. In the basis of submission statement section (1.12.11) of the petitioned ANDA, in addition to identifying the RLD and its application number (as it would for a non-petitioned ANDA), the applicant should reference the FDA-assigned docket number for the approved suitability petition and include a copy of FDA's correspondence approving the suitability petition. Also, the RLD should generally be identified as the reference standard in that section.

⁴⁷ FDA previously has indicated in certain limited circumstances that for drug products for which one NDA holder holds multiple approved NDAs for different strengths of the same drug product, it may be appropriate to accept an ANDA that references more than one NDA number. This promotes a more efficient use of the Agency's review resources. See guidance for industry *Variations in Drug Products that May Be Included in a Single ANDA* (December 1998). As previously noted, if an applicant has a question about which listed drug it should identify as the RLD, the applicant may submit controlled correspondence to seek input from the Agency.

⁴⁸ See Comprehensive Table of Contents Headings and Hierarchy, <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM315023.pdf>, for electronic submissions.

⁴⁹ See, e.g., Attachment 1 of MAPP 5200.14 *Filing Review of Abbreviated New Drug Applications*, which provides technical information on how to organize an ANDA submission.

⁵⁰ See discussion of suitability petitions in the Background section of this guidance.

⁵¹ 21 CFR 314.94(a)(3)(i) and (iii).

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However, if after approval of a suitability petition and before approval of an ANDA submitted pursuant to the approved petition, a drug product is approved in an NDA for the change described in the petition, the suitability petition and the listed drug identified in the petition can no longer be the basis of submission, irrespective of whether FDA has withdrawn approval of the petition. Under these circumstances, an applicant seeking approval for a drug product with the change approved in the suitability petition must submit a new ANDA that identifies the drug product with the same active ingredient, dosage form, route of administration, and strength that has been approved for safety and effectiveness under section 505(c) of the FD&C Act as the RLD and as its basis of submission and comply with applicable regulatory requirements.⁵²

3. Basis of Submission for a Generic Drug That Is a Duplicate of a Drug Product Approved in a Petitioned ANDA

When an ANDA applicant seeks approval of a generic drug that is a duplicate of a drug product in an approved petitioned ANDA (and for which the same drug has not been approved for safety and effectiveness under section 505(c) of the FD&C Act), the basis of submission is the RLD and the approved suitability petition. The ANDA must contain: (1) the name of the RLD, which must be the same as the listed drug identified in the approved suitability petition, and RLD application number; (2) a reference to the suitability petition's FDA-assigned docket number; and (3) a copy of FDA's correspondence approving the suitability petition. The drug product approved under the first petitioned ANDA generally will be selected by FDA as the reference standard and should be used for and identified in the appropriate sections of a subsequent ANDA as the reference standard.

⁵² 21 CFR 314.93(f)(2). See also *Abbreviated New Drug Applications and 505(b)(2) Applications; Final Rule*, 81 FR 69580 at 69621-69622 (October 6, 2016).

APPENDIX 1: QUICK REFERENCE

This appendix summarizes the concepts discussed in this guidance. We recommend that an ANDA applicant refer to the appropriate section of the guidance for more detailed information, as needed.

- The *reference listed drug (RLD)* for an ANDA is the drug product that the proposed generic drug is intended to duplicate and to which the ANDA applicant must refer in its ANDA. FDA designates as RLDs listed drugs approved for safety and effectiveness under section 505(c) of the FD&C Act. The Orange Book identifies which listed drugs have been designated by FDA as RLDs, including some listed drugs in the Discontinued Section of the Orange Book. In the electronic Orange Book, there is a column for RLDs. In the printed version of the Orange Book, RLDs are identified by a distinct symbol.
- The *reference standard* selected by FDA must be used in conducting any in vivo bioequivalence study required for approval of the ANDA. The reference standard may or may not be the same listed drug as the RLD. Other comparisons of the proposed generic drug to determine whether it meets the statutory requirements for approval under section 505(j) of the FD&C Act (e.g., sameness requirements) generally must be to the RLD.

The drug product selected by FDA as the reference standard generally is identified in the Orange Book. In the electronic Orange Book, there is a column for reference standards. In the printed version of the Orange Book, reference standards are identified by a distinct symbol.

- If you mistakenly identify the reference standard as the RLD in your ANDA, you may submit an amendment to a pending ANDA or a supplement to an approved ANDA to correct the information. FDA considers this error to be a deficiency related to identification of the appropriate listed drug as the RLD, rather than a change in the RLD itself. The cover letter for such a submission should clearly identify that the purpose of the submission is “Correction of RLD information.”
- The *basis of submission* statement in an ANDA (e.g., in section 1.12.11 of the ANDA) and in Form FDA 356h (field 20) should include the name of the RLD and the RLD application number. For a petitioned ANDA, the basis of submission statement in the ANDA (e.g., in section 1.12.11 of the ANDA) also should include a reference to the FDA-assigned docket number for the approved suitability petition and a copy of FDA’s correspondence approving the suitability petition. The reference standard, if it is different from the RLD, should be identified in the appropriate sections of the ANDA (e.g., sections 1.12.11, 2.7.1, 5.2, and 5.3.1).

TABLE: REFERENCING APPROVED DRUG PRODUCTS IN AN ANDA

What drug product is the generic drug intended to be the same as?	RLD	Reference Standard	Identification of Basis of Submission in ANDA		Identification of reference standard in ANDA
			Form FDA 356h	ANDA	
ANDA for a generic drug that is a duplicate of its RLD	The RLD is a listed drug approved for safety and effectiveness under section 505(c) of the FD&C Act and identified as an RLD in the Orange Book.	Generally, the RLD also is the reference standard if it is being marketed. The applicant should check the Orange Book to confirm the listed drug that FDA has selected as the reference standard for that drug product.	Fill in the name of RLD and its application number for field 20 on the form.	Identify the RLD and its application number in section 1.12.11.	Identify the reference standard in sections 1.12.11, 2.7.1, 5.2, and 5.3.1 of the ANDA.
ANDA for a generic drug for which a suitability petition has been approved	The listed drug, approved for safety and effectiveness, identified in the approved suitability petition is the RLD.	Generally the listed drug identified in the approved suitability petition is the reference standard.	Fill in the name of RLD and its application number for field 20 on the form.	In section 1.12.11: <ul style="list-style-type: none"> • Identify the RLD and its application number, • Identify the FDA-assigned docket number for the approved suitability petition, and • Include a copy of FDA's correspondence approving the suitability petition 	Identify the reference standard in sections 1.12.11, 2.7.1, 5.2, and 5.3.1 of the ANDA.

TABLE: REFERENCING APPROVED DRUG PRODUCTS IN AN ANDA (cont'd)

What drug product is the generic drug intended to reference?	RLD	Reference Standard	Identification of Basis of Submission in ANDA		Identification of reference standard in ANDA
			Form FDA 356h	ANDA	
ANDA for a generic drug that is the same as a drug product approved in a petitioned ANDA	The listed drug, approved for safety and effectiveness, identified in the approved suitability petition is the RLD.	<p>The drug product approved in the first petitioned ANDA generally is the reference standard.</p> <p>The applicant should check the Orange Book to confirm the listed drug that FDA has selected as the reference standard for that drug product.</p>	Fill in the name of RLD and its application number for field 20 on the form.	<p>In section 1.12.11:</p> <ul style="list-style-type: none"> • Identify the RLD and its application number, • Identify the FDA-assigned docket number for the approved suitability petition, and • Include a copy of FDA's correspondence approving the suitability petition. 	Identify the reference standard in sections 1.12.11, 2.7.1, 5.2, and 5.3.1 of the ANDA.