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Determining Whether to Submit an ANDA or a 505(b)(2) Application Guidance for Industry

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

**May 2019
Generics**

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Determining Whether to Submit an ANDA or a 505(b)(2) Application 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 serve as a foundational guidance to assist applicants in determining which one of the abbreviated approval pathways under the Federal Food, Drug, and Cosmetic Act (FD&C Act) is appropriate for the submission of a marketing application to FDA. Many potential drug product developers are not familiar with the different abbreviated approval pathways for drug products under the FD&C Act — the abbreviated approval pathways described in section 505(j) and 505(b)(2) of the FD&C Act (21 U.S.C. 355(j) and 21 U.S.C. 355(b)(2), respectively) — or the types of data and information that are permitted to support approval under those pathways. In order to familiarize potential drug product developers with these abbreviated pathways, this guidance highlights criteria for submitting applications under the abbreviated approval pathways described in section 505(j) and 505(b)(2), identifies considerations to help potential applicants determine whether an application would be more appropriately submitted under section 505(j) or pursuant to section 505(b)(2) of the FD&C Act, and provides direction to potential applicants on requesting assistance from FDA in making this determination.

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 Drug Price Competition and Patent Term Restoration Act of 1984 (Public Law 98-417) (Hatch-Waxman Amendments) added section 505(b)(2) and 505(j) to the FD&C Act, which

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.

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describes abbreviated approval pathways under the FD&C Act for drug products regulated by the Agency. The Hatch-Waxman Amendments reflect Congress's efforts to balance the need to "make available more low cost generic drugs by establishing a generic drug approval procedure" with new incentives for drug development in the form of exclusivities and patent term extensions.² With the passage of the Hatch-Waxman Amendments, the FD&C Act describes different routes for obtaining approval of two broad categories of drug applications: new drug applications (NDAs) and abbreviated new drug applications (ANDAs).³

NDAs and ANDAs can be divided into the following four categories:⁴

- (1) A "stand-alone NDA" is an application submitted under section 505(b)(1) and approved under section 505(c) of the FD&C Act 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.
- (2) A 505(b)(2) application is an NDA submitted under section 505(b)(1) and approved under section 505(c) of the FD&C Act 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.⁵
- (3) An ANDA is an application submitted and approved under section 505(j) of the FD&C Act for a drug product that is a duplicate⁶ of a previously approved drug product. An ANDA relies on FDA's finding that the previously approved drug product, i.e., the reference listed drug (RLD),⁷ is safe and effective. An ANDA generally must contain information to show that the proposed generic product (1) is the same as the RLD with respect to the active ingredient(s), conditions of use, route of administration, dosage form, strength, and labeling (with certain

² See H.R. Rep. No. 98-857, pt. 1, at 14-15 (1984), reprinted in 1984 U.S.C.C.A.N. 2647-2648.

³ See section 505(b) and 505(j) of the FD&C Act. See generally 21 CFR part 314.

⁴ See letter from Janet Woodcock to Katherine M. Sanzo, Jeffrey B. Chasnow, Stephen E. Lawton, and William R. Rakoczy (October 14, 2003), Docket Nos. FDA-2001-P-0369 (original Docket No. 2001P-0323/CP1 & C5), FDA-2002-P-0390 (original Docket No. 2002P-0447/CP1), and FDA-2003-P-0274 (original Docket No. 2003P-0408/CP1). (Please note that the docket numbers were changed in January 2008 after FDA transitioned to a new docketing system (Regulations.gov).)

⁵ For more information on 505(b)(2) applications, see the draft guidance for industry *Applications Covered by Section 505(b)(2)* (December 1999). When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents>.

⁶ 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.

⁷ The *RLD* "is the listed drug identified by FDA as the drug product upon which an applicant relies in seeking approval of its ANDA." 21 CFR 314.3(b). Because an ANDA applicant is relying upon FDA's finding that the RLD is safe and effective, FDA's practice is to designate as RLDs drug products that have been approved for safety and effectiveness.

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permissible differences) and (2) is bioequivalent to the RLD. An ANDA may not be submitted if clinical investigations are necessary to establish the safety and effectiveness of the proposed drug product.

- (4) A petitioned ANDA is a type of ANDA for a drug product that differs from the RLD in its dosage form, route of administration, strength, or active ingredient (in a product with more than one active ingredient) and for which FDA has determined, in response to a petition submitted under section 505(j)(2)(C) of the FD&C Act (suitability petition), that studies are not necessary to establish the safety and effectiveness of the proposed drug product. A petitioned ANDA is generally expected to provide the same therapeutic effect as the listed drug that was relied on as the basis of the suitability petition.

This guidance focuses on those applications that can be submitted as ANDAs under section 505(j) of the FD&C Act, petitioned ANDAs under section 505(j)(2)(C) of the FD&C Act, or NDAs pursuant to section 505(b)(2) of the FD&C Act. This guidance does not discuss stand-alone NDAs.

A scientific premise underlying the Hatch-Waxman Amendments is that a drug product approved in an ANDA under section 505(j) of the FD&C Act is presumed to be therapeutically equivalent⁸ to its RLD. Products classified as therapeutically equivalent can be substituted with the full expectation that the substituted product will produce the same clinical effect and safety profile as the prescribed product when administered to patients under the conditions specified in the labeling.⁹ In contrast to an ANDA, a 505(b)(2) application allows greater flexibility as to the characteristics of the proposed product. A 505(b)(2) application will not necessarily be rated therapeutically equivalent to the listed drug it references.

III. ABBREVIATED APPROVAL PATHWAYS

A. ANDAs¹⁰

As discussed in section II of this guidance, section 505(j) of the FD&C Act, together with its implementing regulations, generally requires that an ANDA demonstrate that the proposed

⁸ See 21 CFR 314.3(b) (“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.”). See also preface to *FDA’s Approved Drug Products With Therapeutic Equivalence Evaluations* (the Orange Book) (pg. vii-viii, 39th ed.), available at <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/UCM071436.pdf>.

⁹ See preface to the Orange Book (pg. vii, 39th ed.).

¹⁰ Please note that this guidance is intended to assist applicants deciding whether to submit an ANDA or a 505(b)(2) application but does not provide details on the content and format of or the submission process for an ANDA or a 505(b)(2) application. For more information on the content and format of or the submission process for an ANDA, select the “Generics” heading on the FDA guidance web page. For information on the content and format of or the submission process for an NDA, select the “Clinical” and “Procedural” headings on the FDA guidance web page.

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generic drug product and the applicable RLD are the same with respect to their active ingredient(s), dosage form, route of administration, strength, conditions of use, and labeling (with certain exceptions).¹¹ An ANDA must also include sufficient information (1) to demonstrate that the proposed product is bioequivalent to the RLD¹² and (2) to ensure the product's identity, strength, quality, and purity. Consistent with any statutory provisions related to the exclusivity of and patents listed for the RLD, FDA must approve an ANDA unless there is insufficient evidence that these criteria are met.¹³ An ANDA relies on the Agency's finding of safety and effectiveness for an RLD and, as a result, that ANDA may be approved without submission of the same type and extent of information as is required for an NDA to establish the safety and efficacy of the proposed product.¹⁴

Also, as discussed in section II above, an ANDA may contain certain types of differences from an RLD (e.g., a change approved in response to a suitability petition or other permissible differences, such as certain differences in inactive ingredients, labeling, or container closure systems), as long as clinical investigations are not necessary to establish the safety or effectiveness of the drug product proposed in the ANDA.

B. 505(b)(2) Applications

As discussed in section II above, an application submitted through the pathway described in section 505(b)(2) of the FD&C Act 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 use¹⁵ (e.g., the Agency's finding of safety and/or effectiveness for a listed drug, published literature). A 505(b)(2) applicant may rely on FDA's finding of safety and/or effectiveness for a listed drug only to the extent that the proposed product in the 505(b)(2) application shares characteristics (e.g., active ingredient, dosage form, route of administration, strength, indication or other conditions of use) in common with the relied-upon listed drug(s).¹⁶ The applicant is expected to establish a *bridge* (e.g., by using comparative bioavailability data) between the proposed drug product and each listed drug that the applicant seeks to rely upon to demonstrate that reliance on the listed drug is scientifically justified. To the extent that the listed drug and the drug proposed in the 505(b)(2) application differ (e.g., a product with a different dosage form or a product that is intentionally more bioavailable than the listed drug), the

¹¹ See section 505(j)(2)(A) and 505(j)(4) of the FD&C Act and 21 CFR 314.94 and 314.127.

¹² See section 505(j)(2)(A)(iv) and 505(j)(4)(F) of the FD&C Act and 21 CFR 320.21(b).

¹³ See section 505(j)(2)(A) and 505(j)(4) of the FD&C Act and 21 CFR 314.94, 314.105, and 314.127.

¹⁴ See section 505(j)(2)(A) of the FD&C Act.

¹⁵ See 21 CFR 314.3(b) ("Right of reference or use is the authority to rely upon, and otherwise use, an investigation for the purposes of obtaining approval of an NDA, including the ability to make available the underlying raw data from the investigation for FDA audit, if necessary.").

¹⁶ A drug product in a 505(b)(2) application may not necessarily be bioequivalent, pharmaceutically equivalent, and/or therapeutically equivalent to the listed drug(s) relied upon. Generally, *pharmaceutical equivalents* are products that contain the same active ingredient(s), dosage form, route of administration, and strength. See 21 CFR 314.3.

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505(b)(2) application must include sufficient data to support those differences.¹⁷ If FDA has approved one or more pharmaceutically equivalent products in one or more NDAs before the date of the submission of the original 505(b)(2) application, the applicant must identify one such pharmaceutically equivalent product as a listed drug (or an additional listed drug) relied upon but need not provide a scientific bridge to that product unless it is scientifically necessary to support approval.¹⁸

IV. SUBMISSION THROUGH THE APPROPRIATE ABBREVIATED APPROVAL PATHWAY

A. Regulatory Considerations for ANDAs and 505(b)(2) Applications

1. Duplicates

FDA generally will refuse to file a 505(b)(2) application for a drug that is a duplicate of a listed drug and eligible for approval under section 505(j) of the FD&C Act.¹⁹

If FDA approves a pharmaceutical equivalent to a proposed product before a 505(b)(2) application is *submitted*, such that the proposed product would be a duplicate of that pharmaceutically equivalent drug product and eligible for approval under section 505(j) of the FD&C Act, FDA will refuse to file the application as a 505(b)(2) application. However, if FDA approves a duplicate drug product after a 505(b)(2) application is submitted but before the 505(b)(2) application is approved, that application would remain eligible for approval as a 505(b)(2) application, and FDA would not require the applicant of the pending 505(b)(2) application to withdraw the application and submit an ANDA.

2. Petitioned ANDAs

As noted in section II of this guidance, certain differences between an RLD and a proposed generic drug product may be permitted in an ANDA if these differences are the subject of an approved suitability petition.²⁰ An applicant may submit a suitability petition to FDA requesting permission to submit an ANDA for a generic drug product that differs from an RLD in its route of administration, dosage form, or strength or that has one different active ingredient in a fixed-combination drug product.²¹ An ANDA citing a suitability petition that is pending or has been

¹⁷ See 21 CFR 314.54(a). See also letter from Janet Woodcock to Katherine M. Sanzo, Jeffrey B. Chasnow, Stephen E. Lawton, and William R. Rakoczy (October 14, 2003), *supra* note 4.

¹⁸ See 21 CFR 314.50(i)(1)(i)(C), 314.54(a)(1)(iii) and (vi), and 314.125(b)(19). See also 81 FR 69580 at 69620-21 (October 6, 2016).

¹⁹ 21 CFR 314.101(d)(9) (noting that FDA may refuse to file an NDA if the “NDA is submitted as a 505(b)(2) application for a drug that is a duplicate of a listed drug and is eligible for approval under section 505(j) of the [FD&C] Act”).

²⁰ See 21 CFR 314.93.

²¹ See section 505(j)(2)(C) of the FD&C Act and 21 CFR 314.93.

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denied will not be received for review because the application lacks a legal basis for the submission.²²

FDA will approve a suitability petition unless, among other things, (1) it determines that the safety and effectiveness of the proposed change from the RLD cannot be adequately evaluated without data from investigations that exceed what may be required for an ANDA²³ or (2) the petition is for a drug product for which a pharmaceutical equivalent has been approved in an NDA, including, for example, a 505(b)(2) application that referenced the same listed drug named in the suitability petition.²⁴ In the latter case, the ANDA applicant should instead refer to the approved pharmaceutical equivalent designated by the Agency as the RLD as the basis for submission of its ANDA. After approval of an NDA for a drug product that is a pharmaceutical equivalent to the drug product described in the suitability petition, the approved suitability petition (and listed drug described therein) may no longer be used as the basis for an ANDA submission by applicants with pending ANDAs or by prospective ANDA applicants for that petitioned drug product.²⁵ In this scenario, an applicant with a pending ANDA will be required to submit a new ANDA that both identifies the pharmaceutically equivalent product as the RLD and complies with applicable regulatory requirements.²⁶

3. *Bundling*

In some circumstances, an applicant may seek approval for multiple drug products containing the same active ingredient(s) when some of these products would qualify for approval under the section 505(j) pathway and some would qualify for approval under the 505(b)(2) pathway. In these circumstances, FDA has permitted an applicant to submit a single 505(b)(2) application for all such multiple drug products that are permitted to be bundled in a single NDA.²⁷ For example, an applicant seeking approval for multiple strengths of a product, only some of which are included in the Orange Book as listed drugs, would not have to submit both an ANDA for the strengths listed in the Orange Book and a 505(b)(2) application for the new strengths; instead, the applicant may submit one 505(b)(2) application for all of the proposed strengths.

²² See Manual of Policies and Procedures 5240.5 Rev. 1 *ANDA Suitability Petitions*, which is available on the CDER Manual of Policies & Procedures (MAPP) web page at <https://www.fda.gov/about-fda/center-drug-evaluation-and-research/cder-manual-policies-procedures-mapp>. See also the guidance for industry *ANDA Submissions—Content and Format of Abbreviated New Drug Applications* (September 2018) at 8-9.

²³ See section 505(j)(2)(A) and 505(j)(2)(C) of the FD&C Act and 21 CFR 314.93(e)(1)(i).

²⁴ 21 CFR 314.93(e)(1)(vi). See also 21 CFR 314.93(b).

²⁵ 21 CFR 314.93(f)(2).

²⁶ See *ibid.* See also 81 FR 69580 at 69621-22 (October 6, 2016).

²⁷ See the guidance for industry *Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees* (December 2004).

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B. Scientific Considerations for ANDAs and 505(b)(2) Applications

1. Type of Studies, Data, and Information Submitted in ANDAs

Although ANDAs and certain 505(b)(2) applications rely on the Agency's finding of safety and effectiveness for a listed drug, there may be differences in the types of studies, data, and information that may be necessary to support the approval of drug products proposed in ANDAs compared to 505(b)(2) applications. 505(b)(2) applicants have significant flexibility in the types of studies, data, and information they may submit in a 505(b)(2) NDA to support the requirements for NDA approval. The types of studies that may be submitted in a 505(b)(2) NDA may include clinical investigations to establish the safety and/or effectiveness of a product. Generally, ANDA applicants also have significant flexibility in the types of studies, data, and information they may submit in an ANDA to support the requirements for ANDA approval, so long as clinical investigations are not submitted to establish the safety or effectiveness of a product. For example, FDA has accepted limited confirmatory studies appropriate for petitioned ANDAs²⁸ in an original ANDA, and FDA has reviewed pharmacodynamic data in determining active ingredient sameness.²⁹ The precise scope and type of information necessary for approval will vary and may be the subject of discussion between the applicant and FDA during the drug development process.³⁰

If a clinical investigation (i.e., any experiment other than a bioavailability study in which a drug is administered or dispensed to, or used on, human subjects)³¹ is necessary to demonstrate the safety or effectiveness of a proposed drug product, generally this type of study goes beyond the scope of information that may be relied upon as necessary for approval in an ANDA. We recommend that a prospective ANDA applicant considering submission of an application that may require data that could be considered outside of the scope of the ANDA pathway contact the Office of Generic Drugs (OGD) prior to submission of an application to inform which type of application is appropriate.³²

2. Active Ingredient Sameness Evaluation

As stated in sections II. and III.A of this guidance, section 505(j) of the FD&C Act generally requires that a proposed generic drug product demonstrate that it is the same as the RLD with

²⁸ See 54 FR 28872 at 28880 (July 10, 1989) and 57 FR 17950 at 17958 (April 28, 1992).

²⁹ See, for example, the draft product-specific guidance for Enoxaparin Sodium injections, which includes equivalence of the in vivo pharmacodynamic profile as one of the five criteria for demonstrating active ingredient sameness of the test and reference products. When final, this product-specific guidance will represent the FDA's current thinking on this topic. For the most recent version of a product-specific guidance, check the Product-Specific Guidances for Generic Drug Development web page at <https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075207.htm>

³⁰ See section V of this guidance for information about requesting assistance from FDA.

³¹ 21 CFR 314.108(a).

³² See section V of this guidance for information about requesting assistance from OGD.

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respect to active ingredient(s).³³ If the active ingredient in an applicant's proposed drug product cannot be demonstrated to be the same as the active ingredient in the RLD by using the information and data that may be submitted in connection with an ANDA, the drug product should not be submitted for approval in an ANDA.

FDA has broad discretion to determine whether an ANDA applicant has submitted information sufficient for the Agency to reasonably conclude that the proposed drug product's active ingredient is the same as the active ingredient in the RLD.³⁴ That is, the statutory provisions outlining the contents of an ANDA do not describe the type or amount of information that an ANDA applicant must submit to demonstrate that the active ingredient in the proposed generic drug product is the same as the active ingredient in the RLD. In addition, in the preamble to the final rule to implement the Hatch-Waxman Amendments, FDA specifically rejected the adoption of requirements that active ingredients "exhibit the same physical and chemical characteristics [as the RLD], that no additional residues or impurities can result from the different manufacture or synthesis process, and that the stereochemical characteristics and solid state forms of the drug have not been altered."³⁵ Instead, FDA has adopted a more flexible approach.³⁶

In some instances, current limitations of scientific understanding and technology may preclude approval of an ANDA with the data permitted for submission in an ANDA, including, for example, with respect to establishing active ingredient sameness of a given product. As scientific understanding and technology evolve, though, FDA may be able to receive, review, and approve ANDAs where it previously lacked the scientific basis to do so. We therefore recommend that a prospective ANDA applicant with questions about determining active ingredient sameness contact OGD prior to submission of the application.³⁷

3. Intentional Differences Between the Proposed Drug Product and the RLD

a. Differences in formulation

Although section 505(j) of the FD&C Act generally requires that the active ingredient(s) in a proposed ANDA be the same as the active ingredient(s) in the RLD, certain differences in inactive ingredients are permissible. An ANDA must include information regarding the identity and quantity of all active and inactive ingredients of the proposed drug product (i.e., the formulation) and a characterization of any permitted differences between the formulations of the proposed drug product and the RLD, along with a justification demonstrating that the safety and

³³ See section 505(j)(2)(A)(ii) and 505(j)(4)(C) of the FD&C Act.

³⁴ See generally *Serono Laboratories, Inc. v. Shalala*, 158 F.3d 1313 (D.C. Cir. 1998).

³⁵ 57 FR 17950 at 17958-59 (April 28, 1992).

³⁶ *Ibid.* at 17959. See also letter from Janet Woodcock to J. Michael Nicholas (April 16, 2015), Docket No. FDA-2015-P-1050.

³⁷ See section V of this guidance for information about requesting assistance from OGD.

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effectiveness of the proposed drug product is not adversely affected by these differences.³⁸ For products for certain routes of administration, the types of changes to inactive ingredients that are permissible in an ANDA have been limited by regulation.³⁹ For example, in order to qualify for submission as an ANDA:

- Parenteral drug products generally must contain the same inactive ingredients and in the same concentrations as the RLD.⁴⁰ However, specific qualitative and quantitative changes from the RLD formulation are permitted in an ANDA for a parenteral drug product for certain inactive ingredients (i.e., preservatives, buffers, and antioxidants) that are considered *exception excipients*.⁴¹ All other inactive ingredients in a proposed parenteral drug product must be qualitatively and quantitatively the same (Q1/Q2 same) as the RLD.⁴²
- Ophthalmic drug products generally must be Q1/Q2 same as the RLD with respect to all of their inactive ingredients.⁴³ However, an ANDA for an ophthalmic drug product may contain differences from the RLD with respect to certain inactive ingredients (i.e., preservatives, buffers, substances to adjust tonicity, or thickening agents), which are considered *exception excipients*.⁴⁴ To note, for certain ophthalmic drug products, however, FDA has determined that, as a scientific matter, qualitative or quantitative deviations from the RLD in exception excipients may necessitate the need to conduct an

³⁸ 21 CFR 314.94(a)(9)(ii). See also 21 CFR 314.94(a)(5) for active ingredient identity and 21 CFR 314.94(a)(6) for active ingredient strengths.

³⁹ See 21 CFR 314.94(a)(9)(iii) and (iv).

⁴⁰ 21 CFR 314.94(a)(9)(iii).

⁴¹ Ibid. (“However, an applicant may seek approval of a [parenteral] drug product that differs from the reference listed drug in preservative, buffer, or antioxidant provided that the applicant identifies and characterizes the differences and provides information demonstrating that the differences do not affect the safety or efficacy of the proposed drug product.”).

⁴² See 21 CFR 314.94(a)(9)(iii). When an ANDA applicant seeks approval for a parenteral formulation that is the same as that previously marketed by the innovator, FDA has determined that, in appropriate circumstances, pursuant to 21 CFR 314.99(b), it may waive the requirement in the regulation that the inactive ingredients in a parenteral drug product approved under an ANDA be the same as those in the RLD (except for preservatives, buffers, and antioxidants), as long as the statutory requirement regarding safety of inactive ingredients has been met. See section 505(j)(4)(H) of the FD&C Act. In determining whether to grant such a waiver, the Agency considers, among other things, whether the previously marketed formulation was discontinued for reasons of safety or effectiveness. See, e.g., letter from Janet Woodcock to Steven H. Sklar and Peter O. Safir (November 7, 2012), Docket Nos. FDA-2011-P-0339 and FDA-2012-P-0507.

⁴³ See 21 CFR 314.94(a)(9)(iv).

⁴⁴ Ibid. (“However, an applicant may seek approval of a drug product that differs from the reference listed drug in preservative, buffer, substance to adjust tonicity, or thickening agent provided that the applicant identifies and characterizes and provides information demonstrating that the differences do not affect the safety or efficacy of the proposed drug product, except that, in a product intended for ophthalmic use, an applicant may not change a buffer or substance to adjust tonicity for the purpose of claiming a therapeutic advantage over or difference from the listed drug, e.g., by using a balanced salt solution as a diluent as opposed to an isotonic saline solution, or by making a significant change in the pH or other change that may raise questions or irritability.”).

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additional in vivo bioequivalence study (e.g., bioequivalence study with pharmacokinetic endpoints, bioequivalence study with clinical endpoints, as appropriate).⁴⁵

- Otic drug products generally must be Q1/Q2 same as the RLD with respect to all of their inactive ingredients. However, otic drug products may contain differences with respect to the same exception excipients described for ophthalmic drug products.⁴⁶

When an ANDA applicant seeks approval of a parenteral, ophthalmic, or otic drug product that differs from the RLD in its exception excipients, the applicant must identify and characterize the differences and provide information demonstrating that these differences do not affect the safety or efficacy of the proposed drug product.⁴⁷

An applicant should consider submitting a 505(b)(2) application if the proposed drug product contains changes to its formulation that are not permissible in an ANDA. For example, a proposed parenteral drug product that contains an additional inactive ingredient not present in the RLD that cannot be considered an exception excipient would not be permitted in an ANDA under the regulations at 21 CFR 314.94(a)(9)(iii) but may be submitted in a 505(b)(2) application. Similarly, a proposed drug product that contains an excipient that would require clinical investigations to establish safety of the excipient for use in a particular drug product, would also not be permitted in an ANDA but may be submitted in a 505(b)(2) application. We recommend that prospective ANDA applicants (1) consider both the ANDA regulatory requirements for formulations applicable to specific routes of administration and the data that would be scientifically necessary to support any permissible differences in inactive ingredients between the proposed product and the RLD and (2) contact OGD prior to submission of the application to discuss questions about permissible differences in formulation.⁴⁸

b. Differences in bioequivalence and/or bioavailability

An ANDA must contain information to show that the proposed drug product is bioequivalent to the RLD.⁴⁹ A proposed drug product is bioequivalent to the RLD if

the rate and extent of absorption of the [proposed] 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.⁵⁰

Similarly, the definition of *bioequivalence* in the regulations states, in part, that

⁴⁵ See 21 CFR 320.21 and 21 CFR 320.22(b)(1).

⁴⁶ See 21 CFR 314.94(a)(9)(iv).

⁴⁷ See 21 CFR 314.94(a)(9)(iii) and (iv).

⁴⁸ See section V of this guidance for information about requesting assistance from OGD.

⁴⁹ Section 505(j)(2)(a)(iv) and 505(j)(4)(F) of the FD&C Act and 21 CFR 314.94(a)(7)(i).

⁵⁰ Section 505(j)(8)(B)(i) of the FD&C Act. See also 21 CFR 314.3(b).

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[w]here there is an intentional difference in rate (e.g., in certain extended-release dosage forms), certain pharmaceutical equivalents or alternatives may be considered bioequivalent if there is no significant difference in the extent to which the active ingredient or moiety from each product becomes available at the site of drug action.⁵¹

An application for a proposed drug product where the rate and/or extent of absorption exceed, or are otherwise different from, the 505(j) standards for bioequivalence may be submitted under the 505(b)(2) pathway and may require studies to show the safety and efficacy of the proposed product at the different rate and/or extent of delivery.⁵² However, FDA generally will not file a 505(b)(2) application for a drug product

whose only difference from a listed drug is that: (1) [t]he extent to which its active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the listed drug; or (2) [t]he rate at which its active ingredient(s) is absorbed or otherwise made available to the site of action is unintentionally less than that of the listed drug.⁵³

Therefore, a 505(b)(2) application is not appropriate for a drug product that should have been submitted under the ANDA pathway but would have failed to meet all of the 505(j) standards (e.g., the proposed drug product is a duplicate of a listed drug but is unintentionally less bioavailable and fails to demonstrate bioequivalence to the listed drug). Prospective ANDA applicants should contact OGD to discuss any differences in bioequivalence and bioavailability prior to submission of the application.⁵⁴

c. Differences in conditions of use

An application submitted under section 505(j) of the FD&C Act must include a statement that the conditions of use prescribed, recommended, or suggested in the labeling for the proposed drug product have been previously approved for the RLD.⁵⁵ If an applicant has made changes to a proposed 505(j) drug product such that the proposed labeling of the drug product does not reflect the previously approved conditions of use as described in the labeling of the RLD cited in

⁵¹ 21 CFR 314.3(b).

⁵² See 80 FR 6802 at 6855-56 (February 6, 2015) (“However, there are circumstances in which a proposed drug product that is pharmaceutically equivalent to a listed drug (*i.e.*, drug products in the same dosage form and route(s) of administration that contain the same amount of the same active drug ingredient and that meet other applicable standards) is not eligible for approval as an ANDA and must be submitted as an NDA. For example, a proposed extended-release drug product may intentionally differ in its pharmacokinetic profile from a listed drug that is also an extended-release drug product such that the proposed product cannot meet the bioequivalence requirement for ANDAs.”).

⁵³ 21 CFR 314.54(b)(1) and (2).

⁵⁴ See section V of this guidance for information about requesting assistance from OGD.

⁵⁵ 21 CFR 314.94(a)(4)(i).

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the application (e.g., the applicant has proposed a new indication for the proposed drug product), the application could not be approved as an ANDA.⁵⁶ However, FDA will not refuse to approve an ANDA whose labeling excludes (or “carves out”) conditions of use approved for the RLD that may be omitted from the proposed ANDA labeling because of patents or exclusivity.⁵⁷ We recommend that prospective ANDA applicants considering a change that could be construed as a change to the conditions of use of the RLD contact OGD before submission.⁵⁸

4. *Other Differences*

As noted in this guidance, some differences are permitted between an RLD and a proposed product in an ANDA. However, products that differ considerably from the RLD are generally not candidates for approval under the section 505(j) pathway. If differences between a proposed product and its RLD may require submission of data that could be considered beyond the scope of studies that can be reviewed in an ANDA, a prospective ANDA applicant should contact OGD prior to submission of an application to inform which type of application is appropriate.⁵⁹

a. Device Constituents

FDA recognizes that an applicant of a proposed generic drug-device combination product may choose to develop a device constituent part that differs in design from the RLD. We recommend that prospective applicants intending to submit an ANDA for a proposed combination product that includes both a drug constituent part and a delivery device constituent part review the draft guidance for industry *Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA* (January 2017).⁶⁰

b. Labeling

An ANDA must contain

information to show that the labeling proposed for the new drug is the same as the labeling approved for the [RLD]...except for changes required because of differences approved under a [suitability petition]... or because the new drug and the [RLD] are produced or distributed by different manufacturers.⁶¹

⁵⁶ 21 CFR 314.127(a)(2).

⁵⁷ 21 CFR 314.92(a)(1).

⁵⁸ See section V of this guidance for information about requesting assistance from OGD.

⁵⁹ *Id.*

⁶⁰ When final, this guidance will represent the FDA’s current thinking on this topic. We also recommend that a prospective ANDA applicant with questions about proposed generic drug-device combination products contact OGD prior to submission. See section V of this guidance for information about requesting assistance from OGD.

⁶¹ Section 505(j)(2)(A)(v) of the FD&C Act. See also 21 CFR 314.94(a)(8)(iv) (requiring that the labeling for a proposed generic product “be the same as the labeling approved for the [RLD], except for changes required because of differences approved under a [suitability petition]... or because the drug product and the [RLD] are produced or distributed by different manufacturers.” Such permitted differences in labeling include an “omission of an

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The regulations at 21 CFR 314.94(a)(8)(iv) recognize that certain differences in labeling between generic drug products and RLDs may be appropriate because the generic drug product and the RLD are produced or distributed by different manufacturers.⁶² For example, such differences may include “differences in expiration date, formulation, bioavailability, or pharmacokinetics, labeling revisions made to comply with current FDA labeling guidelines or other guidance, or omission of an indication or other aspect of labeling protected by patent or accorded exclusivity.”⁶³ Although the regulations indicate that these identified examples are not the only acceptable differences in labeling between the generic drug product and the RLD, certain differences in labeling will determine whether the proposed drug product should be submitted in an ANDA or a 505(b)(2) application. For example, an ANDA is not appropriate if the proposed drug product would have a new indication or a new dosing regimen as compared to the RLD (e.g., a proposed product would be administered once daily even though the RLD is labeled for administration twice daily).⁶⁴

FDA reviews differences in labeling as part of the ANDA review process. If the differences in labeling between the products are such that they would require clinical investigations to establish the safety or effectiveness of the proposed product or are significant enough that the labeling no longer satisfies the “same” labeling requirement, the proposed drug product should be submitted under section 505(b) of the FD&C Act. In reference to labeling carve-outs as discussed in section IV.B.3.c of this guidance, FDA considers whether an ANDA product that omits the protected information from its labeling would be rendered less safe or effective than the RLD for its remaining non-protected conditions of use.⁶⁵

V. REQUESTING ASSISTANCE FROM FDA

If an applicant is developing a product that is intended to have the same active ingredient(s), conditions of use, route of administration, dosage form, strength, and (with certain permissible differences) labeling as an RLD and has questions about whether the proposed product would be appropriate for submission in an ANDA, the applicant may submit controlled correspondence⁶⁶ to OGD or request a pre-ANDA meeting with OGD. Controlled correspondence is appropriate if an applicant has a specific and targeted inquiry about the generic drug development process. A

indication or other aspect of labeling protected by patent or accorded exclusivity under section 505(j)(5)(F) of the [FD&C] Act.”).

⁶² 21 CFR 314.94(a)(8)(iv). See also 21 CFR 314.127(a)(7).

⁶³ 21 CFR 314.94(a)(8)(iv).

⁶⁴ See also section IV.B.3.c of this guidance.

⁶⁵ See 21 CFR 314.127(a)(7).

⁶⁶ See the draft guidance for industry *Controlled Correspondence Related to Generic Drug Development* (November 2017) for information on the types of inquiries accepted as controlled correspondence and on how to submit controlled correspondence to OGD. When final, this guidance will represent the FDA’s current thinking on this topic.

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pre-ANDA meeting is appropriate for a prospective applicant seeking a dialogue with the Agency on a particular matter that would fall outside the scope of controlled correspondence.⁶⁷ Requests for pre-ANDA meetings should be submitted to GenericDrugs@fda.hhs.gov.

If an applicant is developing a product that has a different active ingredient, conditions of use, route of administration, dosage form, strength, or labeling than a listed drug and/or is proposing a clinical study program and has questions about submission of an application through the 505(b)(2) pathway, the applicant should contact the appropriate Office of New Drugs review division for assistance.⁶⁸

⁶⁷ See the draft guidance for industry *Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA* (October 2017) for information on the enhanced pathway for discussions between FDA and a prospective applicant preparing to submit an ANDA for a complex product as defined in that guidance. When final, this guidance will represent the FDA's current thinking on this topic.

⁶⁸ For more information on contacting the appropriate Office of New Drugs review division for a possible 505(b)(2) application, see FDA's Enhanced Communication web page at <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm327281.htm>.