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

Guidance for Industry

DRAFT GUIDANCE

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

August 2026
Generic Drugs

Revision 1

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Determining Whether to Submit an ANDA or a 505(b)(2) Application Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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 staff 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 described in sections 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 sections 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.

This guidance revises the guidance for industry *Determining Whether to Submit an ANDA or a 505(b)(2) Application* issued in May 2019. When final, this guidance will replace the May 2019 guidance. Changes from the 2019 version include providing additional information on duplicates and eligibility for approval under section 505(j) of the FD&C Act, as well as other updates that are intended to clarify FDA's recommendations to industry.

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.

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

II. BACKGROUND

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

(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.[4]

(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 duplicate[6] 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

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[2] See H.R. Rep. No. 98-857 (Part 1), 98th Cong., 2d Sess. at 14–15 (1984), reprinted in 1984 U.S.C.C.A.N. 2647–2648.

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

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

[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" (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 term *listed drug* is defined 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 505(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" (21 CFR 314.3(b)). The

information to show that the proposed generic drug 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 permissible differences) and (2) is bioequivalent to the RLD.[8] The methods, facilities, and controls for the manufacturing, processing, and packing of the drug must also be adequate to assure and preserve its identity, strength, quality, and purity.[9] An ANDA may not be submitted if clinical investigations (i.e., any experiment other than a bioavailability study in which a drug is administered or dispensed to, or used on, human subjects)[10] 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 drug 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 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.[11] In contrast to an ANDA, a 505(b)(2) application allows greater flexibility as to the characteristics of the proposed drug product. A drug product approved in a 505(b)(2) application will not necessarily be rated therapeutically equivalent to the listed drug it references.[12]

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term *reference listed drug* (*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.

[8] See e.g., sections 505(j)(2)(A) and 505(j)(4) of the FD&C Act.

[9] See e.g., sections 505(j)(2)(A)(vi) and 505(j)(4)(A) of the FD&C Act.

[10] 21 CFR 314.108(a).

[11] See 21 CFR 314.3(b).

[12] FDA generally does not conduct therapeutic equivalence evaluations for every drug product approved in a 505(b)(2) application. For more information on requesting a therapeutic equivalence evaluation, see the draft guidance for industry *Evaluation of Therapeutic Equivalence* (July 2022). When final, this guidance will represent the FDA's current thinking on this topic. When therapeutic equivalence is evaluated, the differences between a drug product approved in a 505(b)(2) application and another listed drug may preclude a finding that the drug products are therapeutically equivalent. See also section 505(j)(7)(A)(v)(I) of the FD&C Act, which sets forth certain

III. ABBREVIATED APPROVAL PATHWAYS

A. ANDAs[13, 14]

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 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).[15] An ANDA must also include sufficient information (1) to demonstrate that the proposed drug product is bioequivalent to the RLD[16] and (2) to ensure the drug's identity, strength, quality, and purity. Consistent with any statutory provisions related to the exclusivity of and patents listed for the RLD in *FDA's Approved Drug Products With Therapeutic Equivalence Evaluations* (the Orange Book), FDA must approve an ANDA unless there is insufficient evidence that these requirements are met.[17] 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 effectiveness of the proposed drug product.[18]

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

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conditions under which FDA evaluates whether an eligible drug product submitted in an application pursuant to section 505(b)(2) of the FD&C Act is therapeutically equivalent to a listed drug relied upon in the 505(b)(2) application.

[13] 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 Generic Drugs 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.

[14] If a prospective applicant needs assistance in determining whether a 505(b)(2) application or ANDA would be more appropriate, the prospective applicant should contact OGD prior to submission of an application to discuss which type of application is appropriate. See section V of this guidance for information about requesting assistance from OGD.

[15] See sections 505(j)(2)(A) and 505(j)(4) of the FD&C Act and 21 CFR 314.94 and 314.127.

[16] See sections 505(j)(2)(A)(iv) and 505(j)(4)(F) of the FD&C Act and 21 CFR 320.21(b).

[17] See sections 505(j)(2)(A) and 505(j)(4) of the FD&C Act and 21 CFR 314.94, 314.105, and 314.127.

[18] See section 505(j)(2)(A) of the FD&C Act.

reference or use[19] (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 drug 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).[20] The applicant is expected to establish a scientific *bridge* (e.g., via 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 product proposed in the 505(b)(2) application differ (e.g., a drug product with a different dosage form or a drug product that is intentionally more bioavailable than the listed drug), the 505(b)(2) application must include sufficient data to support those differences.[21]

If FDA has approved one or more pharmaceutically equivalent drug products in one or more NDAs before the date of the submission of the original 505(b)(2) application, FDA's regulations require the applicant to identify one such pharmaceutically equivalent drug product as a listed drug (or an additional listed drug) relied upon.[22] If the applicant identifies a pharmaceutically equivalent drug product solely to comply with this requirement, the applicant must provide an appropriate patent certification or statement for any patents listed in the Orange Book for that pharmaceutically equivalent drug product, but need not provide a scientific bridge to that pharmaceutically equivalent drug product unless it is scientifically necessary to support approval.[23]

[19] See 21 CFR 314.3(b).

[20] 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. See e.g., 21 CFR 314.3(b) (defining *pharmaceutical equivalents* and *therapeutic equivalents*).

[21] See 21 CFR 314.54(a). See also letter from Janet Woodcock to K. M. Sanzo, J. B. Chasnow, S. E. Lawton, and W. R. Rakoczy, 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) (Oct 14, 2003). (Please note that the docket numbers were changed in January 2008 after FDA transitioned to a new docketing system (Regulations.gov)).

[22] 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 69620–69621 (Oct 6, 2016).

[23] 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 69620–69621 (Oct 6, 2016).

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 product that is a duplicate of a listed drug and eligible for approval under section 505(j) of the FD&C Act.[24, 25]

If FDA approves a drug product under section 505(c) of the FD&C Act before a 505(b)(2) application is submitted for a proposed drug product, such that the proposed drug product would be a duplicate of that previously approved drug product and eligible for approval under section 505(j) of the FD&C Act, FDA generally 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.

When comparative in vivo and/or in vitro studies to demonstrate bioequivalence for a particular drug product, that would otherwise be expected,[26] cannot be conducted in support of an ANDA for a duplicate of a listed drug because (1) the RLD and reference standard[27] are listed in the Orange Book's Discontinued Drug Product List (commonly referred to as the Discontinued Section) and (2) there is no other drug product listed in the Orange Book's Prescription Drug Product List (commonly referred to as the Active Section) that can be designated as a reference standard for that RLD, it might be appropriate for a prospective applicant to consider whether alternate methods to establish bioequivalence are adequate for the proposed drug product to be eligible for approval under section 505(j) of the FD&C Act. In such circumstances, FDA recommends that a prospective applicant contact the Office of Generic Drugs (OGD) prior to submission of the application for the proposed drug product to discuss alternate methods of establishing bioequivalence. See section V of this guidance for information about requesting assistance from OGD.

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[24] 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]").

[25] As discussed in section IV.B of this guidance, a 505(b)(2) application is not appropriate for a drug product that should have been submitted as an ANDA under the 505(j) pathway but differs from the listed drug in bioavailability in certain respects. See 21 CFR 314.54(b).

[26] Certain types of drug products may be eligible for a waiver from conducting in vivo bioequivalence studies that are typically required to support an ANDA. For example, in accordance with 21 CFR 320.22(b)(1), parenteral solutions intended solely for administration by injection, in addition to ophthalmic and otic solutions, may be eligible for a waiver, provided that their formulations are considered qualitatively and quantitatively the same (Q1/Q2 same) as the RLD, because in such instances bioequivalence is considered to be self-evident.

[27] 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 (21 CFR 314.3(b)). Although the regulations do not require that an applicant use a particular drug product for in vitro testing, FDA recommends that the reference standard also be used for in vitro testing. For more information, see the guidance for industry *Referencing Approved Drug Products in ANDA Submissions* (October 2020).

When comparative in vivo and/or in vitro studies to demonstrate bioequivalence for a particular drug product, that would otherwise be expected,[28] cannot be conducted in support of an ANDA for a duplicate of a listed drug because (1) the RLD and reference standard are listed in the Discontinued Section, (2) there is no other drug product listed in the Active Section that can be designated as a reference standard for that RLD, and (3) FDA determines that there are no acceptable alternate methods to establish bioequivalence between the proposed duplicate drug product and the RLD, there may be circumstances in which a prospective applicant can consider submitting a 505(b)(2) application for the proposed drug product.[29, 30] However, there may be limitations on when it would be appropriate to submit a 505(b)(2) application in such circumstances. Therefore, before submitting a 505(b)(2) application, the prospective applicant should discuss its proposal with the appropriate review division in the Office of New Drugs (OND) to ascertain whether a 505(b)(2) application is appropriate. Such discussion should include the prospective applicant's proposed scientific bridge between the proposed drug product and the listed drug (e.g., reliance on published literature), which would be a different approach than the typical approaches for establishing bioequivalence for 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.[31] An applicant can 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.[32] An ANDA citing a suitability petition that is pending or has been denied will not be received for review because the application lacks a legal basis for the submission.[33]

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

[28] See footnote 26.

[29] If FDA determines that there are acceptable alternate methods to establish bioequivalence of the proposed drug product and the RLD notwithstanding (1) the RLD and reference standard being listed in the Discontinued Section and (2) the lack of another drug product listed in the Active Section that can be designed as a reference standard for that RLD, FDA would consider the proposed drug product to be eligible for approval under section 505(j) of the FD&C Act, and FDA generally would refuse to file a 505(b)(2) application for that proposed drug product. See footnote 22.

[30] If the RLD or reference standard moves from the Discontinued Section to the Active Section before a 505(b)(2) application is submitted, in such circumstances, FDA generally will refuse to file the 505(b)(2) application. However, if the RLD or reference standard moves from the Discontinued Section to the Active Section 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 that application and submit an ANDA.

[31] See 21 CFR 314.93.

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

[33] See Manual of Policies and Procedures (MAPP) 5240.5 Rev. 3 *ANDA Suitability Petitions*, which is available on the CDER 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* (June 2019) at section III.A.4.

without data from investigations that exceed what may be required for an ANDA[34] or (2) a drug product is approved in an NDA, including, for example, a 505(b)(2) application, for the change described in the petition.[35] In the latter case, the ANDA applicant must instead refer to the drug product designated by the Agency as the RLD as the basis for submission of its ANDA.[36] After approval of an NDA for a drug product for the change 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.[37] In this scenario, an applicant with a pending ANDA should withdraw the pending ANDA, and FDA will require the applicant to submit a new ANDA that both identifies the pharmaceutically equivalent drug product as the RLD and complies with applicable regulatory requirements.[38]

3. Bundling

In some circumstances, an applicant may seek approval for multiple drug products containing the same active ingredient(s) when some of these drug 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.[39] For example, an applicant seeking approval for multiple strengths of the same dosage form of a drug product, only some of which are duplicates of previously approved drug products 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.

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

1. Types 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 as compared to 505(b)(2) applications. Those submitting 505(b)(2) applications have significant flexibility in the types of studies, data, and information they can submit in a 505(b)(2) application to support the requirements for NDA approval. The types of studies that can be submitted in a 505(b)(2) application may include clinical investigations to establish the safety and/or effectiveness of a drug 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 necessary to establish the safety or effectiveness of a drug product. For example, FDA has accepted limited

[34] See sections 505(j)(2)(A) and 505(j)(2)(C) of the FD&C Act and 21 CFR 314.93(e)(1)(i).
[35] 21 CFR 314.93(e)(1)(vi). See also 21 CFR 314.93(b).
[36] 21 CFR 314.3(b); 21 CFR 314.94(a)(3).
[37] 21 CFR 314.93(f)(2).
[38] Ibid. See also 81 FR 69580 at 69621-22 (October 6, 2016).
[39] See the guidance for industry *Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees* (December 2004).

confirmatory studies appropriate for petitioned ANDAs,[40] and FDA has reviewed pharmacodynamic data in determining active ingredient sameness.[41] 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.[42]

If a clinical investigation 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. A prospective applicant that is considering submission of an application that may require data that could be considered outside of the scope of an ANDA under the 505(j) pathway should contact OGD prior to submission of an application to discuss which type of application is appropriate.[43]

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 an applicant's proposed generic drug product be demonstrated to be the same as the RLD with respect to active ingredient(s).[44] 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 an ANDA, the proposed 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.[45] 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."[46] Instead, FDA has adopted a more flexible approach.[47]

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 drug product. As

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[40] See 54 FR 28872 at 28880 (July 10, 1989) and 57 FR 17950 at 17958 (Apr 28, 1992).
[41] See, for example, the draft product-specific guidance (PSG) on Enoxaparin Sodium injections (October 2011), which includes equivalence of the in vivo pharmacodynamic profile as one of the five criteria for demonstrating active ingredient sameness of the proposed drug product and RLD. When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a PSG, check the Product-Specific Guidances for Generic Drug Development web page at https://www.accessdata.fda.gov/scripts/cder/psg/index.cfm.
[42] See section V of this guidance for information about requesting assistance from FDA.
[43] See section V of this guidance for information about requesting assistance from OGD.
[44] See sections 505(j)(2)(A)(ii) and 505(j)(4)(C) of the FD&C Act. See also the draft guidance for industry *Active Ingredient Sameness in ANDA – Active Ingredients* (November 2022). When final, this guidance will represent the FDA's current thinking on this topic.
[45] See generally *Serono Laboratories, Inc.* v. *Shalala*, 158 F.3d 1313 (D.C. Cir. 1998).
[46] 57 FR 17950 at 17958–17959 (Apr 28, 1992).
[47] Id. at 17959. See also letter from Janet Woodcock to J. M. Nicholas, Docket No. FDA-2015-P-1050 (Apr 16, 2015).

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. Therefore, a prospective ANDA applicant with questions about determining active ingredient sameness should contact OGD prior to submission of an application.[48]

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 drug product in an ANDA be the same as the active ingredient(s) in the RLD, certain differences in inactive ingredients may be 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 effectiveness of the proposed drug product is not adversely affected by these differences.[49] For drug products for certain routes of administration, the types of changes to inactive ingredients that are permissible in an ANDA have been limited by regulation.[50] 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.[51] 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*.[52] All other inactive ingredients in a proposed parenteral drug product must be qualitatively and quantitatively the same (Q1/Q2 same) as the RLD.[53]

[48] See section V of this guidance for information about requesting assistance from OGD.
[49] 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.
[50] See e.g., 21 CFR 314.94(a)(9)(iii) and (iv).
[51] 21 CFR 314.94(a)(9)(iii).
[52] 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.").
[53] See 21 CFR 314.94(a)(9)(iii).

- Ophthalmic drug products generally must be Q1/Q2 same as the RLD with respect to all of their inactive ingredients.[54] 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*.[55] 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 one or more appropriate in vivo bioequivalence studies.[56]

- Otic drug products generally must be Q1/Q2 same as the RLD with respect to all of their inactive ingredients.[57] However, otic drug products may contain differences with respect to the same exception excipients described for ophthalmic drug products.[58]

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 effectiveness of the proposed drug product.[59]

Under 21 CFR 314.99(b), an ANDA applicant may ask FDA to waive any requirement that applies to the applicant under 21 CFR 314.92 through 314.99. FDA has determined that, in appropriate circumstances, pursuant to 21 CFR 314.99(b), it may waive the inactive ingredient requirements in 21 CFR 314.94(a)(9)(iii) and (iv), as long as the statutory requirement regarding safety of inactive ingredients has been met. For example, in certain circumstances, it may be appropriate for FDA to consider a waiver to permit a Q1 or Q2 difference in a pH adjuster(s) in a generic drug product intended for parenteral, ophthalmic, or otic use.[60] As described in 21 CFR 314.99(b), the applicant must comply with the requirements for a waiver under 21 CFR 314.90.[61]

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[54] See 21 CFR 314.94(a)(9)(iv).

[55] 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 of irritability.").

[56] See 21 CFR 320.21 and 21 CFR 320.22(b)(1). See also the relevant PSG. For the most recent version of a PSG, check the Product-Specific Guidances for Generic Drug Development web page at https://www.accessdata.fda.gov/scripts/cder/psg/index.cfm.

[57] See 21 CFR 314.94(a)(9)(iv).

[58] See 21 CFR 314.94(a)(9)(iv). ("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. . . .")

[59] 21 CFR 314.94(a)(9)(iii) and (iv).

[60] See the guidance for industry *Considerations for Waiver Requests for pH Adjusters in Generic Drug Products Intended for Parenteral, Ophthalmic, or Otic Use* (November 2025) for more information on 21 CFR 314.99(b) waivers with regard to a pH adjuster.

[61] As another example, 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

Even if FDA grants a waiver of a requirement in 21 CFR 314.92 through 314.99 for a particular ANDA, the application still must meet all applicable statutory requirements for approval.

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 drug product that contains an inactive ingredient (excipient) that would require clinical investigations to establish safety of the inactive ingredient for use in a particular drug product would not be permitted in an ANDA but may be submitted for approval in a 505(b)(2) application. Prospective ANDA applicants should (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 drug product and the RLD and (2) contact OGD prior to submission of the application to discuss questions about permissible differences in formulation.[62]

b. Differences in bioequivalence and/or bioavailability

An ANDA must contain information to show that the proposed drug product is bioequivalent to the RLD.[63] 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.[64]

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

> [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.[65]

An application for a proposed drug product where the rate and/or extent of absorption intentionally 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

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 S. H. Sklar and P. O. Safir, Docket Nos. FDA-2011-P-0339 and FDA-2012-P-0507 (Nov 7, 2012).

[62] See section V of this guidance for information about requesting assistance from OGD.

[63] Sections 505(j)(2)(a)(iv) and 505(j)(4)(F) of the FD&C Act, and 21 CFR 314.94(a)(7)(i).

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

[65] 21 CFR 314.3(b).

efficacy of the proposed drug product at the different rate and/or extent of absorption.[66] 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.[67]

Therefore, a 505(b)(2) application is not appropriate for a proposed drug product that 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.[68]

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.[69] If information submitted with the ANDA is not sufficient to show that each of the proposed conditions of use has been previously approved for the RLD (e.g., the applicant has proposed a new indication for the proposed drug product), the application could not be approved as an ANDA.[70] 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.[71] Prospective ANDA applicants considering a change that could be construed as a change to the conditions of use of the RLD should contact OGD before submission.[72]

4. Other Differences

As noted in this guidance, some differences are permitted between an RLD and a proposed drug product in an ANDA. However, proposed drug products that differ considerably from the RLD are generally not candidates for approval under the section 505(j) pathway. If the differences between a proposed drug product and its RLD require submission of data that could be considered beyond the scope of studies that can be reviewed in an ANDA, a prospective ANDA

[66] See 80 FR 6802 at 6855–6856 (Feb 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.").
[67] 21 CFR 314.54(b)(1) and (2).
[68] See section V of this guidance for information about requesting assistance from OGD.
[69] 21 CFR 314.94(a)(4)(i).
[70] 21 CFR 314.127(a)(2).
[71] See e.g., 21 CFR 314.92(a)(1).
[72] See section V of this guidance for information about requesting assistance from OGD.

applicant should contact OGD prior to submission of an application to discuss which type of application is appropriate.[73]

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. FDA recommends that prospective applicants intending to submit an ANDA for a proposed combination product that includes both a drug constituent part and a 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).[74]

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.[75]

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.[76] 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."[77] 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 drug product would be administered once daily even though the RLD is labeled for administration twice daily).[78]

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[73] Ibid.

[74] When final, this guidance will represent the FDA's current thinking on this topic. FDA also recommends 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.

[75] 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 drug 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." Under this regulation, such permitted differences in labeling include an "omission of an indication or other aspect of labeling protected by patent or accorded exclusivity under section 505(j)(5)(F) of the [FD&C Act]."). See also 21 CFR 314.127(a)(7).

[76] 21 CFR 314.94(a)(8)(iv). See also 21 CFR 314.127(a)(7).

[77] 21 CFR 314.94(a)(8)(iv).

[78] See also section IV.B.3.c of this guidance.

FDA reviews differences in labeling as part of the ANDA review process. If the differences in labeling between the drug products are such that they would require clinical investigations to establish the safety or effectiveness of the proposed drug product or are significant enough that the labeling no longer satisfies the *same* labeling requirement, an ANDA would not be appropriate for approval of the proposed drug product, and the applicant should instead consider submitting a 505(b)(2) application. In reference to labeling carve-outs as discussed in section IV.B.3.c of this guidance, FDA considers whether an ANDA drug product that omits the protected information from its labeling would be rendered less safe or effective than the RLD for its remaining nonprotected conditions of use.[79]

V. REQUESTING ASSISTANCE FROM FDA

If an applicant is developing a drug 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 drug product would be appropriate for submission in an ANDA, the applicant can submit controlled correspondence[80] 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 pre-ANDA meeting is appropriate for a prospective applicant seeking advice from the Agency on a particular matter that would fall outside the scope of controlled correspondence.[81] Requests for pre-ANDA meetings should be submitted electronically through the CDER Direct NextGen Collaboration Portal.[82]

If an applicant is developing a drug product that has a different route of administration, dosage form, or strength, or active ingredient (in a drug product with more than one active ingredient) than the RLD and the difference is the subject of an approved suitability petition, the applicant can submit controlled correspondence to OGD with questions about developing the drug pursuant to the approved suitability petition.[83]

If an applicant is developing a drug 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 development program and has questions about submission of an application

[79] See 21 CFR 314.127(a)(7).
[80] See the guidance for industry *Controlled Correspondence Related to Generic Drug Development* (March 2024) for information on the types of inquiries accepted as controlled correspondence and on how to submit controlled correspondence to OGD.
[81] See the guidance for industry *Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA* (October 2022) 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.
[82] The CDER Direct NextGen Collaboration Portal may be accessed at https://edm.fda.gov/. See the guidance for industry *Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA* for more information on the requests for pre-ANDA meetings.
[83] See footnote 81. See also the guidance for industry *Referencing Approved Drug Products in ANDA Submissions* (October 2020) and section IV.A.2 of this guidance for more information on petitioned ANDAs.

through the 505(b)(2) pathway, the applicant should contact the appropriate OND review division for assistance.[84]

[84] For more information on contacting the appropriate OND review division for a possible 505(b)(2) application, see FDA's Enhanced Communication web page at https://www.fda.gov/industry/prescription-drug-user-fee-amendments/enhanced-communication and the OND Review Division Contact Information document at https://www.fda.gov/media/78312/download?attachment.