

CHRONICLES

SEPTEMBER 19TH, 2019

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Featuring Elizabeth Friedman, JD, LLM
Regulatory Counsel, Office of Generic
Drugs

Resources:

1. [Determining Whether to Submit an ANDA or 505\(b\)\(2\) Application – Guidance for Industry](#)
2. [2019 Generic Drug Forum Conference Presentation: 505\(b\)\(2\) NDA or ANDA?](#)
3. [Drug Competition Action Plan](#)

Upcoming Events:

1. [REdI and CERSI Workshop: Current State and Future Expectations of Translational Modeling Strategies to Support Drug Product Development, Manufacturing Changes and Controls – Sept. 23-25 - College Park, MD](#)
2. [REdI: 2019 Complex Generic Drug Product Workshop – Sept. 25-26 – College Park, MD](#)
3. [REdI: Pharmaceutical Quality Symposium – October 16-17 - College Park, MD](#)

Abbreviated Approval Pathways for Drug Products: 505(b)(2) or ANDA?

Determining the right abbreviated approval pathway for submitting a drug product application to FDA requires an understanding of the options available and what types of data are permitted to support a selection.

The Drug Price Competition and Patent Term Restoration Act of 1984 (also known as the Hatch-Waxman Amendments) added sections 505(b)(2) and 505(j) to the Federal Food, Drug, and Cosmetic Act (FD&C Act), establishing abbreviated routes for obtaining approval for new drug applications (NDAs) and abbreviated new drug applications (ANDAs). FDA's final guidance for industry "[Determining Whether to Submit an ANDA or 505\(b\)\(2\) Application](#)" assists prospective applicants and provides direction in determining which one of these pathways is more appropriate.

A 505(b)(2) application is an NDA that contains full reports of investigations of safety and effectiveness, where at least some of the information required for approval comes from studies not conducted by or for the applicant, and for which the applicant has not obtained a right of reference or use, including, for example, the Agency's finding of safety and/or effectiveness for a listed drug or published literature. NDAs requiring 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, known as "stand-alone" NDAs, are submitted under section 505(b)(1) of the FD&C Act.

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 of a previously approved drug product. It relies on FDA's finding that the previously approved drug product (the reference listed drug or RLD), is safe and effective, and may not be submitted if clinical investigations are necessary to establish the safety and effectiveness of the proposed drug product. An ANDA generally must contain information to show that the proposed generic product 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 is bioequivalent to the RLD.



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Considerations for submission of ANDAs and 505(b)(2) applications include the following situations:

Drug product is a duplicate of the RLD: FDA generally will refuse to file a 505(b)(2) application for a drug that is a duplicate of an already listed drug and eligible for approval as an ANDA.

Drug product differs from the RLD: 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 (see [21 CFR 314.93](#)).

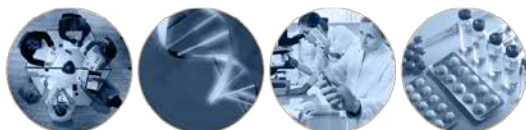
Multiple drug products contain the same active ingredient(s): An applicant may seek approval for multiple drug products containing the same active ingredient(s) when some of these products would qualify for approval under the section 505(j) pathway and some would qualify for approval under the 505(b)(2) pathway. In this case, the applicant may bundle these drug products by submitting a single 505(b)(2) application. 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, may submit one 505(b)(2) application for all of the proposed strengths.

The types of studies, data and Information that may be necessary to support the approval of drugs proposed in ANDAs compared to 505(b)(2) applications may differ. For example, 505(b)(2) applications may include clinical investigations to establish the safety and/or effectiveness of a product. Generally, ANDA applicants 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. 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.

Active ingredient sameness is evaluated to demonstrate that the proposed generic drug product is the same as the RLD with respect to active ingredient(s). As scientific understanding and technology evolve, FDA may be able to receive, review, and approve ANDAs where it previously lacked the scientific basis to do so.

Intentional differences between the proposed drug product and the RLD, such as differences in formulation, bioequivalence and/or bioavailability, and conditions of use should be considered.

- ***Formulation:*** An ANDA generally may differ from the RLD in inactive ingredients. However, the ANDA must include information regarding the identity and quantity of all active and inactive ingredients of the proposed drug product. It must also include 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. If the proposed drug product contains changes to its formulation that are not permissible in an ANDA, the applicant should consider submitting a 505(b)(2) application. For example, a proposed drug product that contains an excipient that requires clinical investigations to establish safety of the excipient would not be permitted in an ANDA but may be submitted in a 505(b)(2) application.
- ***Bioequivalence/bioavailability:*** An ANDA must contain information to show that its rate and extent of absorption does not show a significant difference from that of the RLD. If there is an intentional difference in rate (such as in certain extended-release dosage forms), certain pharmaceutical equivalents or alternatives may be considered bioequivalent if there is no significant difference in the extent of absorption. A 505(b)(2) application may be submitted if the rate and/or extent of absorption exceed, or are different from the ANDA standards, and may require studies to show safety and efficacy. However, FDA a 505(b)(2) application is generally not appropriate for a



drug product that should have been submitted under the ANDA pathway, but would have failed to meet the 505(j) standards. For example, a 505(b)(2) application may not be appropriate if 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.

- *Conditions of Use:* An ANDA must include a statement that the conditions of use in the labeling for the proposed drug product have been previously approved for the RLD. If the proposed labeling reflects different conditions of use than the RLD labeling, such as a new indication, the application could not be approved as an ANDA. However, the ANDA labeling may exclude (or “carve out”) conditions of use approved for the RLD that may be omitted from the proposed ANDA labeling because of patents or exclusivity.

Clearly, some differences are permitted between an RLD and a proposed product in an ANDA. For example, certain differences in labeling between generic drug products and RLDs, such as 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, may be allowed. However, products that differ considerably from the RLD or require submission of data that could be considered beyond the scope of studies that can be reviewed in an ANDA are generally not candidates for approval under the 505(j) pathway.

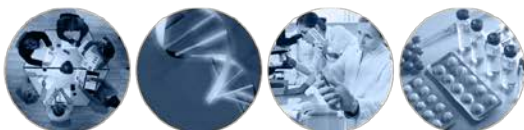
Requesting assistance from FDA: FDA encourages prospective applicants with questions about whether their proposed drug product is appropriate for submission in an ANDA to contact the Office of Generic Drugs before submission. [Controlled correspondence](#) should be used if the applicant has a specific question about the generic drug development process. A [pre-ANDA meeting](#) is appropriate when a prospective applicant would like to discuss with the Agency a particular matter that would fall outside the scope of controlled correspondence. Questions about submission of an application through the 505(b)(2) pathway should be directed to the appropriate [Office of New Drugs review division](#).

The guidance was published as part of the agency’s [Drug Competition Action Plan](#), and to assist in clarifying the ANDA submission process, provide assistance to potential applicants, and ultimately expand access for patients to lower cost, while providing high quality medicine. In addition to the guidance for industry “[Determining Whether to Submit an ANDA or 505\(b\)\(2\) Application](#),” learn more about this topic in our [2019 Generic Drug Forum Conference presentation](#).

Cheers,
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CDER Small Business and Industry Assistance

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This communication is consistent with 21CFR10.85(k) and constitutes an informal communication that represents our best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of the FDA, and does not bind or otherwise obligate or commit the agency to the views expressed.



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