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

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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) (Abbreviated New Drug Application (ANDA) to the FD&C Act, which describe abbreviated approval pathways. 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).

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

NDA
A New Drug Application (NDA - 505b(1)) 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.

505b(2)
A 505(b)(2) application is an NDA that contains full reports of investigations of safety and effectiveness, where at least some of the information required for approval comes from studies not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use (e.g., the Agency's finding of safety and/or effectiveness for a listed drug, published literature). 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 505(b)(2) application must include sufficient data to support those differences.

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 upon approval.

ANDA
An Abbreviated New Drug Application (ANDA – 505(j)) relies on FDA's finding that the previously approved drug product, i.e., the reference listed drug (RLD), is safe and effective. 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)

- is bioequivalent to the RLD. An ANDA may not be submitted if studies are necessary to establish the safety and effectiveness of the proposed product.

> 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.

A scientific premise underlying the Hatch-Waxman Amendments is that a drug product approved in an ANDA is presumed to be therapeutically equivalent to its RLD. They 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.

Petitioned ANDA

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 suitability petition that studies are not necessary to establish the safety and effectiveness of the proposed drug product. An ANDA citing a suitability petition that has not been approved will not be received for review because the application lacks a legal basis for the submission.

Regulatory and Scientific Considerations for ANDAs and 505(b)(2) Applications

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 a ANDA.

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. 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.

Limited Confirmatory Studies

Although ANDAs and certain 505(b)(2) applications rely on the Agency's finding of safety and effectiveness for a listed drug, any additional information that may support the approval of the proposed drug product may differ between these two submissions. In certain instances, limited confirmatory clinical studies may be acceptable in an ANDA if the purpose of those studies is not to establish safety and effectiveness.

Intentional Differences Between the Proposed Drug Product and the RLD

Differences in formulation

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. 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.

Differences in bioequivalence and/or bioavailability
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. However, a 505(b)(2) application is not appropriate for a drug product that should have been submitted under the ANDA pathway but 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).

Differences in conditions of use
An ANDA 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.
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 (e.g., the proposed drug product has added a new indication), the application could not be approved as an ANDA. However, FDA will not refuse to approve an ANDA whose labeling excludes conditions of use approved for the RLD that may be omitted from the proposed ANDA labeling because of patents or exclusivity.

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.

Certain differences in labeling between generic drug products and RLDs (e.g., differences in the products' expiration dates, formulation, bioavailability, or pharmacokinetics; labeling revisions made to comply with current FDA labeling guidelines or guidance; or the omission of an indication or other aspect of labeling protected by patent or exclusivity) may be appropriate because the generic drug product and the RLD are produced or distributed by different manufacturers. Though 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

Differences in labeling between the proposed generic product and the RLD must not render the proposed drug product less safe or effective than the RLD. If the differences between the products are such that they would require investigations to establish the safety or effectiveness of the proposed product or necessitate such significant labeling differences that the labeling no longer satisfies the same labeling requirement, the proposed drug product should be submitted under a 505(b)2.