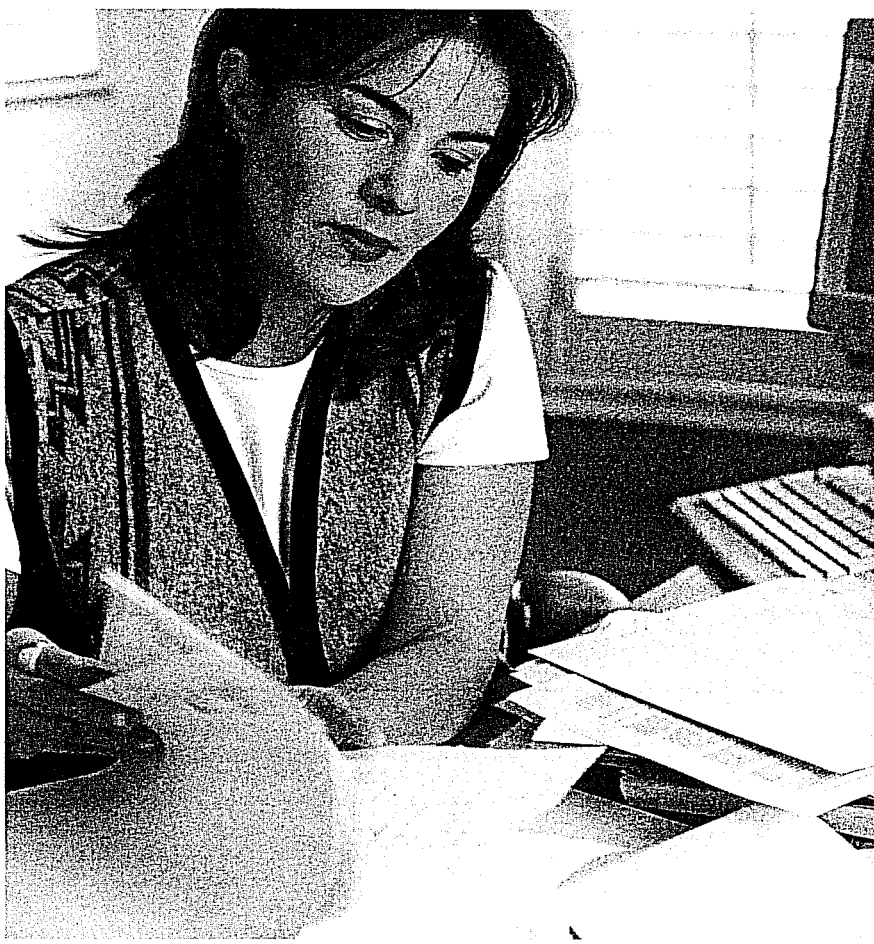
To "(b)(2)" or Not to "(b)(2)"?

When a 505(b)(2) Is Not an ANDA



By Dolores R. Massari, MS

The regulatory line between 505(b)(2) new drug applications (NDAs) and abbreviated new drug applications (ANDAs) appears to blur at times, since the two types of applications share many characteristics. When an applicant other than the sponsor wants to submit changes to an approved (listed) drug, the nature and extent of the potential changes need to be carefully evaluated to determine if the changes qualify for a suitability petition and subsequent ANDA submission, or if a 505(b)(2) application should be submitted. The applicant should also consider the marketing advantages and disadvantages associated with each type of application.

Table 1. Comparison of 505(b)(2) and ANDA applications

Elements of Application	505(b)(2)	ANDA
Complete application	Yes	No
Not all of the information required for approval is from studies conducted by or for the applicant	Yes	Yes
Applicant has not obtained a right of reference to the original data	Yes	Yes
Bioequivalence study required	Yes	Yes
Applicant can rely on the following information to support approval:		
Literature	Yes	No
FDA's previous finding of safety and effectiveness for an approved drug (listed drug)	Yes	Yes
New clinical trial data	Yes	No
Drug is the same as the listed drug	Maybe	Yes*
Approval is subject to patent exclusivity limitations	Yes	Yes

*Some drug changes allowed for an ANDA if a suitability petition is approved.

An ANDA cannot be submitted for an application that would be submitted as a 505(b)(2), and vice versa, with one exception. The one exception is that a 505(b)(2) may be submitted for a change in drug product that is eligible for consideration as a suitability petition under Section 505(j)(2)(c). A comparison of 505(b)(2) applications and ANDAs is shown in **Table 1**.

ANDAs

An ANDA may be submitted for a copy of an approved listed drug as long as it is the same as the listed drug and does not meet the criteria for either a 505(b)(1) or 505(b)(2) application. The regulations define "same as" as identical in active ingredient(s), dosage form, strength, route of administration and conditions of use.

However, some changes in a generic drug are permitted if a suitability petition is submitted to the Food and Drug Administration (FDA) for the change, and FDA approves the petition. The types of changes to a listed drug for which FDA may approve suitability petitions are the following:

- Route of administration
- Dosage form
- Dosage strength
- One active ingredient is substituted for one of the active ingredients in a listed combination drug

Although suitability petitions may be approved for these types of changes, the decision about granting a suitability petition is based on the determination of whether any other clinical data beyond bioequivalence and bioavailability and/or any preclinical data will be required for approval.

505(b)(2) NDA Submission

Consistent with the draft guidance for 505(b)(2) applications, changes in either the active ingredient or formulation that would change the impurity profile or degradation products would necessitate toxicology studies to support approval as described in International Conference on Harmonisation guidance *Q3A(R): Impurities in New Drug Substances* and *Q3B(R): Impurities in New Drug Products*, and therefore would not be appropriate as ANDA submissions.

The types of changes to a listed drug that are permitted under Section 505(b)(2) or under the ANDA regulations are shown in **Table 2**.

Bioequivalence

If a change to a listed drug is submitted as a 505(b)(2) application, it must meet the following biopharmaceutics requirements:

- The proposed product must be *at least* as bioavailable as the approved reference product (unless it has some other advantage, such as a smaller peak/trough ratio); and
- The pattern of release of the proposed product, although different, must be at least as favorable as the approved reference product.

For an ANDA, a study is required to show bioequivalence to the approved reference-listed drug. The regulations specifically prohibit the submission of a 505(b)(2) for a drug product when the only difference from the reference-listed drug is that it is less bioavailable or is not bioequivalent.

New Indications

The regulations do not permit submission of a new indication for a listed drug as an ANDA because review of clinical data is required to support approval. If an applicant has the rights to all the data for a new indication, the NDA would be submitted under Section 505(b)(1). If some of the studies the applicant was going to rely on for approval were not conducted by the applicant and no right

of reference had been obtained, the NDA would be submitted as a 505(b)(2) application as long as there are no patent infringements.

Labeling

At the time the application is submitted, the applicant is required to include annotated proposed labeling. The label for an ANDA must be the same as that for the reference-listed drug, except if changes were approved under a 505(j)(2)(c) petition or there are differences arising from manufacturing [21 CFR Part 314.94(a)(8)]. However, the label for a drug under a 505(b)(2) application can be quite different. For example, the following information may be added to the label of the reference-listed drug under a 505(b)(2) application:

- New clinical efficacy and safety data;

Table 2. Changes Allowed in 505(b)(2) Applications and ANDAs

Allowed Changes From Approved Listed Drug	505(b)(2)	ANDA
Dosage form	Yes	Yes*
Route of administration	Yes	Yes*
Dosage strength	Yes	Yes*
Active ingredient	Yes	Yes*
Combination product in which one active ingredient is substituted	Yes	Yes*
Formulation	Yes	No
Combination product where active ingedients have been approved individually	Yes	No
Dosing regimen	Yes	No
Rx/OTC switch	Yes	No
The only difference from the reference-listed drug is that the rate or extent of absorption is equal to or less than that of the listed drug	No	Yes
The rate or extent of absorption exceeds that of the reference-listed drug	Yes	No
New indication	Yes	No
New information may be added to the package insert	Yes	No

*If a suitability petition is approved, an ANDA may be used if no data beyond bioequivalence or bioavailability are required to support approval.

- New pharmacokinetic and bioavailability data; and
- New nonclinical data.

Marketing Advantages

A 505(b)(2) NDA for an NCE may be eligible for five years of exclusivity under the Hatch-Waxman Amendments. Similarly, a 505(b)(2) NDA for a new indication could be eligible for three years of exclusivity, if clinical studies were required for the approval and the studies were conducted by the applicant. Additionally, the results of clinical studies could be used to support the promotional platform for the product. None of these are available for ANDAs. However, the first applicant to file an ANDA containing a paragraph IV certification to a listed patent may be eligible for 180 days of exclusivity.

Summary

Some changes to a listed drug are clearly beyond the scope of changes for which suitability petitions will be approved by FDA. However, in other cases, careful evaluation of the changes to be incorporated, the data that will be required to support approval of the changes and the desired marketing claims is needed to determine the appropriate submission route.

RECOMMENDED READING
21 CFR Part 314.54. Procedure for submission of an application requiring investigation for approval of a new indication for, or other change from, a listed drug.
21 CFR Part 314.92. Drug products for which abbreviated applications may be submitted.
21 CFR Part 314.93. Petition to request a change from a listed drug.
Draft Guidance for Industry, Applications Covered by Section 505(b)(2) (October 1999).
FDA Guidance, *Q3A(R): Impurities in New Drug Substances.*
FDA Guidance, *Q3B(R): Impurities in New Drug Products*.

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