Referencing Approved Drug Products in ANDA Submissions

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Learning Objectives

- Describe FDA's draft guidance *Referencing Approved Drug Products in ANDA Submissions*
- Recognize key terms including a listed drug, a reference listed drug, a reference standard, and the basis of submission
- Identify the basis of submission for a specific Abbreviated New Drug Application (ANDA)

General Framework for ANDAs

- Approval of generic drug starts with a listed drug – generally an innovator drug approved under section 505(c) of the Federal Food, Drug & Cosmetic (FD&C) Act
- ANDA relies on FDA's finding of safety and effectiveness for Reference Listed Drug (RLD)
- Requires demonstration of "sameness" of a number of characteristics to the RLD and additional information to permit reliance on RLD

Evidence to Support Approval of an ANDA

Among other things, an applicant must generally show that its proposed generic drug:

- Has the same active ingredient(s), conditions of use, route of administration, dosage form, strength, and (with certain permissible differences) labeling as the RLD;
- Is bioequivalent to the RLD; and
- Meets the same high standards of quality and manufacturing as new drug products approved under new drug applications (NDAs).

Definitions

- Listed drug
- Reference listed drug
- Reference standard
- Basis of submission

Listed Drug

- A “listed drug” is a new drug 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505(c) of the FD&C Act for safety and effectiveness or under section 505(j) of the FD&C Act, and which has not been withdrawn for reasons of safety or effectiveness.
- A drug product is deemed to be a listed drug on the date of approval.
- Identified in FDA’s *Approved Drug Products with Therapeutic Equivalence Evaluations* (commonly referred to as the Orange Book)

Reference Listed Drug

- An RLD is the specific listed drug on which the ANDA applicant relies in seeking approval of its ANDA, i.e., the approved drug product the proposed generic drug is intended to duplicate.
- FDA identifies in the Orange Book listed drugs that are eligible to be RLDs.

Choosing an RLD

- An ANDA applicant must choose an RLD.
- If the applicant has a question about which listed drug it should identify as the RLD, the applicant may submit a controlled correspondence to FDA prior to submission of its ANDA.
- If FDA has not designated an RLD for the drug product the ANDA applicant intends to duplicate, the applicant may submit controlled correspondence to FDA asking it to designate an RLD for that drug product.

RLD for a Petitioned ANDA

An ANDA applicant may submit an ANDA for a generic drug that is not the *same* as its RLD because:

- It has one different active ingredient (in a fixed combination drug product), or
- It has a different route of administration, dosage form, or strength than that of the RLD

RLD for a Petitioned ANDA

- The applicant must first obtain permission from FDA through the citizen petition process.
- Such petitions are referred to as *suitability petitions*.
- The RLD for a “Petitioned ANDA” must be the same as the listed drug identified in the approved suitability petition.

The Role of an RLD in an ANDA

- The RLD is the listed drug to which the ANDA applicant must show its proposed generic drug is the same with respect to active ingredient(s), dosage form, route of administration, strength, conditions of use, and (with certain permissible exceptions) labeling.

- The ANDA applicant must also demonstrate that the proposed generic drug is bioequivalent to the RLD.

- If the applicant seeks to change its RLD, the applicant must submit a new ANDA.

Reference Standard

- If bioequivalence is not self-evident, there are a variety of methods by which bioequivalence may be demonstrated, including in vivo studies (in human subjects), in vitro studies (conducted in a laboratory), or both.
- 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 of an ANDA.

FDA's Selection of a Reference Standard

- FDA generally selects a single reference standard to ensure the greatest level of consistency between a generic drug and its RLD and among generic drugs.
- If the RLD is marketed, ordinarily it is also selected by FDA as the reference standard.
- If the RLD has been discontinued from marketing other than for safety or effectiveness reasons, FDA may select a different approved drug to serve as the reference standard (generally a previously approved ANDA that referred to the RLD).

Basis for ANDA Submission

- Regulations require an ANDA to contain a “basis for ANDA submission” (referred to as the basis of submission or BOS).
- The RLD should be provided as the BOS on Form FDA 356h and in the appropriate sections of the ANDA (e.g., section 1.12.11).

Basis of Submission – Petitioned ANDAs

The basis of submission for a petitioned ANDA is:

(1) the RLD, which must be the same as the listed drug identified in the approved suitability petition;

(2) a reference to the suitability petition's FDA-assigned docket number; and

(3) a copy of FDA's correspondence approving the suitability petition.

Basis of Submission and the Reference Standard

If the reference standard is not the RLD, it should be identified in the relevant sections of the ANDA that include information pertaining to bioequivalence, e.g.,

- section 1.12.11 which provides information about the drug product including bioequivalence, and
- 2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods.

Challenge Question #1

Which of the following is an ANDA applicant *not* required to provide:

A. Evidence that the proposed generic drug meets the same high standards of quality and manufacturing as new drug products approved under new drug applications

B. Evidence that the proposed generic drug has the same active ingredient(s), conditions of use, route of administration, dosage form, strength, and (with certain permissible differences) labeling as the RLD

C. Evidence that the proposed generic drug is bioequivalent to the RLD

D. Independent evidence of the safety and effectiveness of the proposed generic drug

Challenge Question #2

A Reference Standard is:

A. The drug product selected by FDA that an applicant seeking approval of an ANDA must use in conducting an in vivo bioequivalence study

B. The subject of a suitability petition

C. The specific listed drug on which the ANDA applicant relies in seeking approval of its ANDA

D. Always the same as the RLD

If you have further questions, we encourage you to refer to the draft guidance *Referencing Approved Drug Products in ANDA Submissions* at https://www.fda.gov/regulatory-information/search-fda-guidance-documents


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