U.S. FOOD & DRUG ADMINISTRATION

Considerations for Application Pathway: 505(b)(2) or ANDA

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Overview

- Applications under section 505 of the Federal Food, Drug, and Cosmetic Act (FD&C Act)
- Considerations for Appropriate Abbreviated Approval Pathway – 505(b)(2) NDA or ANDA
- Requesting Assistance From FDA

Applications Under Section 505 of the FD&C Act

Four different routes for obtaining approval of two broad categories of drug applications (NDAs and ANDAs) under the FD&C Act

1. Stand-alone New Drug Applications (NDAs)
2. 505(b)(2) NDAs
3. Abbreviated New Drug Applications (ANDAs)
4. Petitioned ANDAs

Stand-Alone NDAs

- Submitted under 505(b)(1) and approved under 505(c)
- Contain full reports of investigations of safety and effectiveness
- All data necessary for approval was developed by or for the sponsor or for which the sponsor has a right of reference

505(b)(2) NDAs

- Submitted pursuant to 505(b)(2) and approved under 505(c)
- Contain full reports of investigations of safety and effectiveness
- 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, which could include published literature, clinical data produced by other entities, or an agency safety/effectiveness finding for another drug

505(b)(2) NDAs

- Include a “bridge” between the proposed drug product and each listed drug that the applicant seeks to rely upon to demonstrate such reliance is scientifically justified
- Leverage existing knowledge
- Approval may be delayed by patents or exclusivities

ANDAs

- Background
  - Submitted and approved under 505(j)
  - Duplicate of a previously approved drug (reference listed drug (RLD)) that relies on FDA's finding that the RLD is safe and effective
  - Demonstrate sameness to the RLD with respect to active ingredient(s), dosage form, route of administration, strength, previously approved conditions of use, and labeling (with certain exceptions)

ANDAs

- Background (cont'd)
  - Include sufficient information to demonstrate bioequivalence to the RLD
  - May contain certain differences from an RLD as long as investigations are not necessary to establish safety and effectiveness

ANDAs

- Active Ingredient Sameness
  - 505(j) generally requires that a proposed generic drug product demonstrate that it is the same as the RLD with respect to active ingredient(s)
  - *Active ingredient* is any component intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body of man

ANDAs

- Same Labeling
  - ANDA product labeling generally must be the same as the labeling approved for the RLD
  - Certain exceptions:
    - Changes required because of differences approved pursuant to a suitability petition (21 CFR 314.93)
    - Omissions of an indication or other aspect of labeling that is protected by patent or exclusivity
    - Differences because the generic and RLD are produced or distributed by different manufacturers

ANDAs

- Bioequivalence
  - A drug shall be considered to be bioequivalent to a listed drug if the rate and extent of absorption of the drug do not show a significant difference from that of the listed drug.
  - Bioequivalence (BE) may be demonstrated with in vivo or in vitro data, or both
    - Measure active ingredient or moiety in blood, plasma, etc.
    - Measure pharmacodynamic effect
    - Comparative clinical endpoint BE studies
    - Dissolution and formulation data
    - Any other approach deemed appropriate by FDA

Petitioned ANDAs

- What is a suitability petition? A request to submit an ANDA for a drug that is different from the RLD in:
  - Route of administration
  - Dosage form
  - Strength
  - One different active ingredient in a fixed-dose combination drug product
- Petition must be submitted *and* approved before ANDA can be submitted

Petitioned ANDAs

- Suitability petition is submitted to FDA
  - Reviewed per process outlined in MAPP 5240.5 ANDA Suitability Petitions
  - Approved unless FDA identifies reason under 21 CFR 314.93(e)(1) not to approve
- Once approved, an ANDA with that change can be submitted
- Petitioned ANDA submitted under 505(j)(2)(C)

Considerations for Appropriate Abbreviated Approval Pathway

- Depends on many considerations, including:
  - Regulatory considerations, such as:
    - Duplicates
    - Petitioned ANDAs
    - Bundling
  - Scientific considerations, such as:
    - Limited confirmatory studies
    - Active ingredient sameness evaluation
    - Intentional differences between proposed product and RLD

Regulatory Considerations

- Duplicates
  - FDA will refuse to file a 505(b)(2) application for a drug that is a duplicate and eligible for approval under 505(j)
  - If FDA approves a pharmaceutical equivalent to a proposed product ***before*** a 505(b)(2) application is submitted, FDA will refuse to file the application as a 505(b)(2) application
  - If FDA approved a duplicate product ***after*** a 505(b)(2) application is submitted, but before it is approved, the application would remain eligible for approval as a 505(b)(2) application

Regulatory Considerations

- Petitioned ANDAs
  - FDA will approve a suitability petition unless:
    - Safety and effectiveness of the proposed change cannot be adequately evaluated without data from investigations that exceed what may be required for an ANDA; or
    - The petition is for a drug product for which a pharmaceutical equivalent has been approved in an NDA (including a 505(b)(2) application)

Regulatory Considerations

- Petitioned ANDAs (cont'd)
  - Once an NDA for a drug product reflecting the change described in the suitability petition is approved, the suitability petition (and listed drug described in the petition) may no longer be the basis for ANDA submission.

Regulatory Considerations

- Bundling
  - An applicant seeking approval for multiple drug products containing the same active ingredient(s) –
    - Some of these products would qualify for approval under 505(j) and some would qualify for approval under 505(b)(2)
  - May submit one 505(b)(2) application for all proposed products

Scientific Considerations

- Limited Confirmatory Studies
  - Both ANDAs and 505(b)(2) applications may include additional information to support approval
  - For 505(b)(2)s, the types of studies may include clinical investigations to establish the safety and/or effectiveness of a product

Scientific Considerations

- Limited Confirmatory Studies (cont'd)
  - For ANDAs, limited confirmatory clinical studies may be acceptable if the purpose is not to establish safety and effectiveness
  - If the safety and effectiveness must be established by investigations, these investigations go beyond the scope of a limited confirmatory study that may be submitted in an ANDA

Scientific Considerations

- Active Ingredient Sameness Evaluation
  - FDA has broad discretion to determine whether an ANDA contains information sufficient to conclude that the proposed drug's active ingredient is the same as the active ingredient in the RLD.
  - If the active ingredient cannot be demonstrated to be the *same* as the active ingredient in the RLD by using information and data that may be submitted in an ANDA, the proposed drug product should not be submitted for approval in an ANDA.

Scientific Considerations

- Differences in Formulation
  - Certain differences between a proposed drug product in an ANDA and its RLD are permissible
  - ANDA must include:
    - Information regarding the identity and quantity of all active and inactive ingredients
    - A characterization of any permitted differences between the formulations of the proposed drug product and the RLD
    - A justification demonstrating that the safety and effectiveness is not adversely affected by these differences

Scientific Considerations

- Differences in Formulation (cont'd)
  - Applicants can consider a 505(b)(2) application if the proposed drug product contains changes to its formulation not permissible in an ANDA, e.g.,
    - A proposed parenteral drug product that contains an additional inactive ingredient not present in the RLD that cannot be considered an exception excipient
    - A proposed drug product that contains a novel excipient that requires clinical testing to establish safety

Scientific Considerations

- Differences in Bioequivalence and/or Bioavailability
  - A 505(b)(2) application is not appropriate for a drug product that should have been submitted as an ANDA but failed to meet all of the 505(j) standards
  - Example: FDA would refuse to file a 505(b)(2) application if the proposed drug product is a duplicate of a listed drug but is unintentionally less bioavailable and fails to demonstrate BE to the listed drug

Scientific Considerations

- Differences in Conditions of Use
  - An ANDA must include a statement that the conditions of use prescribed, recommended, or suggested in the labeling have been previously approved for the RLD
  - If changes to a proposed generic drug product are such that the proposed labeling of that drug product does not reflect previously approved conditions of use for the RLD, the application cannot be approved as an ANDA

Scientific Considerations

- Labeling
  - Certain differences in labeling between generic products and RLDs are permissible
  - 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
    - The differences between the products are such that they would require investigations to establish the safety or effectiveness of the proposed product or necessitate~~s~~ such significant labeling differences that the labeling no longer satisfies the “same” labeling requirement

Requesting Assistance from FDA

If an applicant is developing a drug product:	And has questions about:	Contact:
• Intended to have the same active ingredient, conditions of use, route of administration, dosage form, strength, and (with certain permissible differences) labeling as an RLD, • And is proposing a nonclinical study program	Qualification of an ANDA	Office of Generic Drugs
• That has a different active ingredient, condition of use, route of administration, dosage form, strength, or labeling than a listed drug • And is proposing a clinical program	Submission through the 505(b)(2) pathway	Office of New Drugs

Challenge Question # 1

A suitability petition must be submitted and approved before an ANDA citing that petition can be submitted?

a. True

b. False

Challenge Question # 2

For a 505(b)(2) application, which of the following is true:

a. It contains full reports of investigations of safety and effectiveness
b. It's approval may be delayed by patents or exclusivities
c. It is a duplicate of a previously approved drug
d. Both A and B

Resources

- Guidance for industry *Determining Whether to Submit an ANDA or a 505(b)(2) Application* (May 2019)
- Guidance for industry *Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA* (October 2022)
- Draft guidance for industry *Controlled Correspondence Related to Generic Drug Development* (December 2022)
- FDA's Enhanced Communication web page[1]
- MAPP 5240.5 ANDA Suitability Petitions (October 2020)

1. http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm327281.htm

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