U.S. FOOD & DRUG ADMINISTRATION

Draft Guidance for Industry:

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

Guidance Purpose and Goals

- Foundational guidance for applicants
- Assist in determining which one of the abbreviated approval pathways under the FD&C Act is appropriate for the submission of a marketing application
- Intended for those potential drug product developers not familiar with the abbreviated approval pathways in 505(j) and 505(b)(2)

Guidance Purpose and Goals (cont'd)

- Highlights criteria for submitting applications under 505(j) and 505(b)(2)
- Identifies considerations to help determine whether an application would be more appropriately submitted under 505(j) or 505(b)(2)
- Provides direction to applicants requesting assistance from FDA

Approval Pathways

Four different routes for the two broad categories of drug applications under the FD&C Act	
1.	Stand-alone new drug application (NDA) submitted under 505(b)(1) and approved under 505(c)
2.	505(b)(2) NDA submitted under 505(b)(2) and approved under 505(c
3.	Abbreviated new drug application (ANDA) submitted and approved under (505(j))
4.	Petitioned ANDA submitted under 505(j)(2)(C) and approved under 505(j)

Abbreviated Approval Pathways

- ANDA
  - Application for a duplicate of a previously approved drug product (the reference listed drug (RLD)) that relies on FDA's finding that the RLD is safe and effective
  - Demonstrates 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)
  - Includes 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

Abbreviated Approval Pathways

- 505(b)(2) NDA
  - 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
  - May rely on FDA's finding of safety and/or effectiveness to the extent that the proposed drug product shares characteristics with the listed drug
  - Includes 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

Submission Through the Appropriate Abbreviated Approval Pathway

Regulatory Considerations
Duplicates
Petitioned ANDAs
Bundling

Scientific Considerations
Limited confirmatory studies
Active ingredient sameness evaluation
Intentional differences between the proposed drug product and the RLD
Other differences

Regulatory Considerations

- Duplicates
  - FDA will refuse to file a 505(b)(2) application for a drug that is a duplicate and should be submitted in an ANDA
  - 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 approves 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
  - Suitability petitions request permission to submit an ANDA that differs from an RLD in:
    - Route of administration,
    - Dosage form,
    - Strength, or
    - One different active ingredient in a fixed-combination drug product
  - An ANDA citing a suitability petition that has not been approved will not be received

Regulatory Considerations

- Petitioned ANDAs (cont'd)
  - 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) that referenced the same listed drug

Regulatory Considerations

- Petitioned ANDAs (cont'd)
  - Once an NDA for a drug product that is a pharmaceutical equivalent to the drug 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 the 505(j) pathway and some would qualify for approval under the 505(b)(2) pathway
  - May submit **one** 505(b)(2) application for all proposed products

Scientific Considerations

- Limited Confirmatory Studies
  - ANDAs and 505(b)(2) applications may include additional information to support the approval
  - Limited confirmatory clinical studies may be acceptable in an ANDA 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
  - 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)
  - 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

- Active Ingredient Sameness Evaluation (cont'd)
  - 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
  - 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

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)
  - Consider a 505(b)(2) application if the proposed drug product contains changes to its formulation not permissible in an ANDA
    - 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
  - Bioequivalent: 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 proposed drug product where the rate and/or extent of absorption are different from the 505(j) standards for BE may be submitted under the 505(b)(2) pathway

Scientific Considerations

- Differences in BE and/or BA (cont'd)
  - 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 the previously approved conditions of use, the application could not be approved as an ANDA

Scientific Considerations

- Labeling
  - Certain differences in labeling between generic drug products and RLDs may be appropriate due to different manufacturers
    - Expiration date
    - Formulation
    - Bioavailability or pharmacokinetics
    - Labeling revisions made to comply with current FDA labeling guidelines
    - Omission of an indication or other aspect of labeling protected by patent or exclusivity

Scientific Considerations

- Labeling (cont'd)
  - 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 such significant labeling differences that the labeling no longer satisfies the "same" labeling requirement

Requesting Assistance

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
- 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 study program	Submission through the 505(b)(2) pathway	Office of New Drugs

Please contact CDERSBIA@fda.hhs.gov with any questions. Thank you.