U.S. FOOD & DRUG ADMINISTRATION

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

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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) application 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)

Comparing the 3 Applications

505(b)(1) NDA	505(b)(2) Application	ANDA
Preclinical	Preclinical	
Clinical	Clinical	
Pediatric Use	Pediatric Use	
Chemistry, Manufacturing, Controls (CMC)	CMC	CMC
Pharmacokinetics (PK) & Bioavailability	PK, Bioavailability, Comparative Bioavailability	Bioequivalence
Labeling	Labeling	Labeling
Patent Information	Patent Information	
	Patent Certification (if applicable)	Patent Certification
Exclusivity Request	Exclusivity Request	
	Exclusivity Statement	Exclusivity Statement

ANDA

- Application for a duplicate of a previously approved drug product (the RLD)
- Demonstrates sameness to the RLD with respect to:

Active ingredient(s)	**Dosage form**
Route of administration	**Strength**
Previously approved conditions of use	**Labeling (with certain exceptions)**

- Includes sufficient information to demonstrate BE
- May contain certain differences from an RLD *as long as* investigations are not necessary to establish safety and effectiveness

505(b)(2) Application

- Contains full reports of investigations of safety and effectiveness
- At least some of the information comes from:
  - Studies not conducted by or for the applicant
  - Studies for which the applicant has not obtained a right of reference
- Includes a “bridge” between the proposed drug product and each source of information that the applicant seeks to rely upon to demonstrate such reliance is scientifically justified

Reliance + Bridging/BE Studies

505(b)(2) Application	ANDA
Applicant must identify all sources of information relied on for approval • NDA listed drug(s), literature, OTC monograph. Does *not* have to rely on Reference Listed Drug (RLD) or Reference Standard (RS) • Can rely on >1 listed drugs and/or >1 sources of information • Must rely on a pharmaceutically equivalent (PE) drug product if PE is approved prior to submission of original 505(b)(2) application	Applicant must identify the previously approved drug product it seeks to duplicate • Specifically, the duplicate product identified as the RLD in the Orange Book
Bridge for listed drug reliance: • Typically BA/BE studies comparing proposed drug to relied upon drug(s) • If relying on a discontinued listed drug; bridging studies should use the RS	Applicant must use the designated RS for use in conducting any in vivo BE testing required to demonstrate bioequivalence • RS is usually the RLD

Submission Through the Appropriate Abbreviated Approval Pathway

Regulatory Considerations
Duplicates
Petitioned ANDAs
Bundling
Scientific Considerations
Information that may be submitted in an ANDA
Active ingredient sameness evaluation
Intentional differences between the proposed drug product and the RLD
Other differences

Regulatory Considerations – Duplicates

- FDA will RTF a 505(b)(2) application for a drug product that is a duplicate of a listed drug

- 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:

1. Route of administration,	**3. Strength, OR**
2. Dosage form,	**4. 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 not approve an suitability petition if:
  - the safety and effectiveness of the proposed change cannot be evaluated without data that exceed what may be submitted in an ANDA, or
  - it is for a drug product for which a pharmaceutical equivalent has been approved in an NDA
- *Applicant's choice*
  - An applicant may submit a 505(b)(2) application for a change in a drug product that is eligible for consideration as an ANDA pursuant to a suitability petition

Regulatory Considerations – Bundling

- An applicant seeking approval for multiple drug products containing the same active ingredient(s)

  Meaning that 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 – Information to Support Approval

505(b)(2) Application	ANDA
Contains information to support the differences between the proposed drug product and the listed drug	May contain additional data and studies to support approval, so long as the purpose is not to establish safety and effectiveness
	NOTE: Investigations to establish safety and effectiveness go beyond the scope of what is permitted in an ANDA

Scientific Considerations – Active Ingredient Sameness Evaluation

- A proposed generic drug product is generally the same as the RLD with respect to active ingredient(s)

- A proposed drug product should not be submitted in an ANDA if the active ingredient cannot be demonstrated to be *the same as* the active ingredient in the RLD by using information that may be submitted in an ANDA

Scientific Considerations - Difference in Formulation

- 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

- Consider submitting a 505(b)(2) application if the proposed drug product contains changes to formulation not permissible in an ANDA
  - *Example*: A proposed parenteral drug product that contains an additional inactive ingredient not present in the RLD that cannot be considered an exception excipient
  - *Example*: A proposed drug product that contains a novel excipient that requires clinical testing to establish safety

Scientific Considerations – Differences in BE and/or BA

- A proposed drug product where the rate and/or extent of absorption are different from the 505(j) standards for BE may be appropriate for submission as a 505(b)(2) application

- But, 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

Scientific Considerations – Differences in Conditions of Use

- ANDA must include a statement that the conditions of use prescribed, recommended, or suggested in the labeling have been previously approved for the RLD

- A proposed drug product should not be submitted in an ANDA if changes to the product are such that the proposed labeling of that drug product does not reflect the RLD's approved conditions of use

Scientific Considerations – Device Constituent Parts

- A proposed generic drug-device combination product may have a device constituent part that has some differences in design from the RLD
- Before submitting an ANDA for a proposed combination product that includes a drug constituent part and a delivery device constituent part → review the draft guidance for industry *Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA*

Scientific Considerations – Labeling

505(b)(2) Application	ANDA
Labeling does not have to be the same as the RLD or listed drug relied upon	Must contain information to show that the labeling proposed for the new drug product is the same as the labeling approved for the RLD
	Certain permissible differences in labeling 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

- Consider a 505(b)(2) application if:
  - The proposed drug product would have a new indication or a new dosing regimen
  - The differences between the products would require investigations to establish the safety or effectiveness of the proposed product
  - The differences between the products require such significant labeling differences that the labeling is no longer the “same” as for the RLD

Requesting Assistance

If an applicant is developing a drug product:	And has questions on:	Contact:
- Intended to have the same active ingredient, conditions of use, route of administration, dosage form, strength, and (with certain 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 or nonclinical study program	Submission through the 505(b)(2) pathway	Office of New Drugs

Requesting Assistance

- For potential ANDAs:
  - Controlled correspondence is appropriate for specific and targeted inquiries about the generic drug development process
    - Draft guidance for industry *Controlled Correspondence Related to Generic Drug Development*
  - A pre-ANDA meeting is appropriate for a dialogue with the Agency on a particular matter that falls outside the scope of controlled correspondence
    - Draft guidance for industry *Formal Meetings Between FDA and Applicants of Complex Products Under GDUFA*
- For potential 505(b)(2) applications:
  - A pre-NDA meeting is appropriate for dialogue with the Agency on the development and review of a new drug product
    - Draft guidance for industry *Formal Meetings Between FDA and Sponsors or Applicants of PDUFA Products*

References

- Draft Guidance for Industry "Determining Whether to Submit an ANDA or a 505(b)(2) Application" (Oct 2017)
- Draft Guidance for Industry "Applications Covered by Section 505(b)(2)" (Oct 1999)

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