Drug-Device Combination Products in ANDAs

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Modern Generic Drug Approval Pathway


- First statutory provisions expressly pertaining to generic drugs
- Created the basic scheme under which generic drugs are approved today
- Allowed FDA to approve - under new section 505(j) - generic applications for duplicates of drugs approved under 505(c)
Foundations of Generic Drug Approval

• Approval of generic drug starts with a “listed drug” – generally an “innovator” drug approved under 505(c)

• ANDA relies on FDA’s finding of safety and effectiveness for listed drug.

• Requires demonstration of “sameness” of a number of characteristics + additional information to permit reliance on the reference listed drug (RLD)
Contents of an ANDA: 505(j)(2)

- Identify Single Listed Drug = Reference Listed Drug (RLD)
- Identify Approved Conditions of Use
- Evidence Supporting:
  - Same Active Ingredient
  - Same Route of Administration
  - Same Dosage Form
  - Same Strength
  - Bioequivalence
  - Safety of Inactive Ingredients
Contents of an ANDA (cont.)

• Chemistry, Manufacturing, and Controls (CMC) Information
  • Components and composition
  • Manufacturing and controls
  • Batch formulation and records
  • Description of facilities
  • Specifications and tests
  • Packaging
  • Stability
• Side-by-Side Comparison of Approved and Proposed Labeling
• Patent Certifications, Exclusivity Information
Same Labeling

- ANDA product labeling generally must duplicate listed drug, except for conditions of use protected by patent or exclusivity.
- Use codes in Orange Book describe scope of patents claiming methods of use.
- ANDA applicant may not omit labeling that is not protected.
- Permissible differences include differences due to different manufacturers.
- May differ in excipients, PK data and how supplied.
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.

• For locally acting drugs, FDA may establish alternative methods if they are expected to detect a significant difference between the drug and the listed drug in safety and therapeutic effect.
Bioequivalence (cont.)

• Bioequivalence may be demonstrated by in vivo or in vitro data, or both:
  - measure active ingredient or moiety in blood, plasma, etc.
  - measure pharmacodynamic effect
  - comparative clinical trials
  - dissolution and formulation data
  - any other approach deemed appropriate by FDA
CGMPs

• ANDAs are held to same high standards for CGMPs as NDAs (e.g., 21 CFR 4)
• Purpose - to assure quality of marketed drug products
• Mechanisms - Product Testing
  • Surveillance
  • Manufacturing/Testing plant inspections
  • Assess firm’s compliance with good manufacturing processes
NDA vs. ANDA Review Process

Brand Name Drug
NDA Requirements
1. Chemistry
2. Manufacturing
3. Controls
4. Labeling
5. Testing
6. Animal Studies
7. Clinical Studies
8. Bioavailability

Generic Drug
ANDA Requirements
1. Chemistry
2. Manufacturing
3. Controls
4. Labeling
5. Testing
6. Bioequivalence
Therapeutic Equivalence Listed in Orange Book

• TE = pharmaceutical equivalent and bioequivalent for same use
• Pharmaceutical equivalent -- same active ingredient in the same dosage form, same strength or concentration, and same route of administration
Same General Principles Apply to Drug-Device Combination Products Submitted in an ANDA
General Principles

• Drug products that are approved in ANDAs are generally considered by FDA to be therapeutically equivalent (TE) to their RLD.
  – A generic drug-device combination product classified as therapeutically equivalent to the RLD can be expected to produce the same clinical effect and safety profile as the RLD under conditions specified in labeling

• Proposed generic drug-device combination product and its RLD do NOT need to be IDENTICAL in all respects
  – However, applicants should generally seek approval of a presentation approved for the RLD

• Considerations
  – Performance characteristics
  – User Interface
General Principles

• In general, the FDA expects that the end-users can use the generic drug-device combination product when it is substituted for the RLD
  – Without additional intervention of the health care provider and/or
  – Without additional training prior to the use of the generic combination product
Performance Characteristics

• Proposed generic product should be comparable to its listed drug in terms of performance

• Examples (comparative assessments)
  – Ejection time
  – Trigger force
  – Needle integrity post-injection
  – Delivered volume
  – Aerodynamic particle size distribution
  – Single actuation content
User Interface

Refers to all components of a product with which a user interacts, such as labels and packaging, the delivery device constituent part, and any associated controls and displays.
Threshold Analyses

• **Labeling Comparison**
  – Side-by-side, line-by-line comparison of the full prescribing information, instructions for use, and descriptions of the delivery device constituent part(s) of the generic drug-device combination product and its RLD.

• **Comparative Task Analysis**
  – Comparative task analysis between the proposed generic drug-device combination product and its RLD.
  – Critical tasks are user tasks that, if performed incorrectly or not performed at all, would or could cause harm to the patient or user, where harm is defined to include compromised medical care.

• **Physical Comparison of Delivery Device Constituent Part**
  – Examine (e.g., visual and tactile examination) the physical features of the delivery device constituent part for the proposed generic drug-device combination product and compare them to those of the RLD.
Assessment of Identified Differences

• Minor Differences
  – Guidance describes a design difference as minor if the differences in the user interface of the proposed generic combination product, in comparison to the user interface of the RLD, do not affect an external critical design attribute. External critical design attributes are those features that directly affect how users perform a critical task that is necessary in order to use or administer the drug product.

• Other Differences
  – FDA may not view a design difference as minor if any aspect of the threshold analyses suggests that differences in the design of the user interface of a proposed generic combination product as compared to the RLD may impact an external critical design attribute that involves administration of the product.
Assessment of Identified Differences

• In instances when differences other than minor differences are identified:
  – Consider re-design of the user interface to minimize differences from the RLD
  – Potential need for additional information and/or data to support the ANDA submission
  • Draft guidance recommends that potential applicants contact FDA through a pre-ANDA submission/controlled correspondence before conducting comparative use human factors studies
Comparative Use Human Factors Studies
Answering A Different Question

• Traditional HF Validation Studies
  – Question 1: Does the proposed user interface support the safe and effective use of the product by intended users for intended uses and environments of use?

• Comparative HF Studies
  – Question 2: Do user interface design difference(s) between a generic and the RLD impact the clinical effect or safety profile of the proposed generic product?
Comparative Use HF Studies

• Objective
  – To demonstrate that the use error rate, associated with a change in an external critical design attribute for the proposed user interface, does not preclude approval of the proposed product in an ANDA
  
  • Non-inferiority design: Comparison of rates of errors observed when using the proposed generic combination product when compared to the use error rates when using the RLD with respect to a critical task impacted by a change in critical external design attribute
  
  • Designed to provide sufficient data to confirm that the use error rate for the proposed generic combination product is not worse than the corresponding use error rate for the RLD when used by patients and caregivers in representative use scenarios and use environments consistent with the labeled conditions of use
Key Takeaways

• Potential applicants should consider the design of the user interface of a proposed generic drug-device combination product in the early phases of development.

• Potential applicants are strongly encouraged to engage with FDA through controlled correspondence and/or pre-ANDA meeting requests in the early phases of development.

• FDA does not expect that the design of a generic drug-device combination product be identical to the design of its RLD.

• Potential applicants should seek to minimize any design differences between the user interface of a proposed generic drug-device combination product and its RLD.

• Allows for flexibility in the types of information and/or data that may be warranted to assess the impact of any differences in design between the user interface of the proposed generic drug-device combination product and its RLD.

• The assessment for therapeutic equivalence includes multiple considerations, including the impact of any design differences between the user interface for a proposed generic drug-device combination product and its RLD.
Questions?