Overview of Drug-Device Combination and What Constitutes Complex Drug-Device Combination

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General Framework For ANDAs

- Approval of generic drug starts with a listed drug – generally an innovator product approved under 505(c)
- An abbreviated new drug application (ANDA) relies on FDA's finding of safety and effectiveness for listed drug
- Requires demonstration of "sameness" of a number of characteristics and additional information to permit reliance on the reference listed drug (RLD)

Contents Of An ANDA

- Identify Single RLD
  - Same Conditions of Use
  - Same Active Ingredient
  - Same Route of Administration
  - Same Dosage Form
  - Same Strength
  - Same Labeling
  - Bioequivalence
- Safety of Inactive Ingredients
- Patent Certifications, Exclusivity Information
- Chemistry, Manufacturing, and Controls Information

Same Labeling

- Generic drug product labeling generally must be the same as the RLD
- Certain limited exceptions
  - Changes required because of differences approved pursuant to a suitability petition
  - Differences because the generic and RLD are produced or distributed by different manufacturers
  - Omissions of an indication or other aspect of labeling that is protected by patent or exclusivity

Current Good Manufacturing Practices

- ANDAs are held to the same high standards for current good manufacturing practices (cGMP) as new drug applications (NDAs)
- Regulatory Citations
  - See 21 CFR 210/211
  - See also 21 CFR 4
    - Clarifies which cGMP requirements apply to combination products

Therapeutic Equivalence

- In relation to the RLD, generic products are expected to be:
  - Pharmaceutically Equivalent
    - The same active ingredient, dosage form, strength, route of administration and meet the same compendial standards (strength, quality, purity, and identity)
  - Bioequivalent
    - No significant difference in the rate and extent of absorption of the active ingredient at the site of action
  - Therapeutically Equivalent
    - Approved drug products that are pharmaceutical equivalents for which bioequivalence has been demonstrated, and that can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling

What Is A Combination Product?

21 CFR 3.2

1. A product comprised of two or more regulated components, i.e., drug/device, biologic/device, drug/biologic, or drug/device/biologic, that are physically, chemically, or otherwise combined or mixed and produced as a single entity;
2. Two or more separate products packaged together in a single package or as a unit and comprised of drug and device products, device and biological products, or biological and drug products;
3. A drug, device, or biological product packaged separately that according to its investigational plan or proposed labeling is intended for use only with an approved individually specified drug, device, or biological product where both are required to achieve the intended use, indication, or effect and where upon approval of the proposed product the labeling of the approved product would need to be changed, e.g., to reflect a change in intended use, dosage form, strength, route of administration, or significant change in dose; or
4. Any investigational drug, device, or biological product packaged separately that according to its proposed labeling is for use only with another individually specified investigational drug, device, or biological product where both are required to achieve the intended use, indication, or effect.

Primary Mode Of Action (PMOA)

- A combination product is assigned to a Center that will have primary jurisdiction for that product's premarket review and regulation
- Based on a determination of which constituent part provides the PMOA of that product
  - PMOA: the single mode of action expected to make the greatest contribution to the overall intended therapeutic effects
- Applicants may submit a request for designation to obtain a binding classification/assignment or a "Pre-RFD" to obtain informal feedback relating to the classification/assignment

Citizen Petitions

- FDA previously discussed the assessment of differences between a proposed generic combination product and its RLD in two citizen petitions:
  - FDA Response to King Pharmaceuticals (Jul. 29, 2009) (Docket No. FDA-2007-P-0128/Docket No. FDA-2009-P-0040)
    - Auto-injectors/Imitrex (sumatriptan succinate)
  - FDA Response to Dey Pharma L.P. (May 27, 2010) (Docket No. FDA-2009-P-0578)
    - Emergency-use auto-injectors/Epipen (epinephrine)

Historical Policy

- Topics generally raised in citizen petitions included:
  - Device constituent physical characteristics
  - Device constituent performance
  - Product labeled instructions for use
  - Therapeutic equivalence for generic auto-injector products

Where Are We Today?

- Considerations include, but are not limited to:
  - Performance characteristics
    - FDA takes into consideration the performance of the device constituent and its interaction and impact on the delivery of the drug constituent
  - User Interface
    - Draft guidance for industry, *Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA* (Jan 2017)
    - This guidance clarifies certain aspects of the citizen petition responses

User Interface

- Applicants should generally seek approval of a presentation approved for the RLD
- FDA does not expect that the design of the user interface for a generic combination product be identical to its RLD's design in all respects
- FDA may accept such design differences if they are adequately analyzed, scientifically justified, and do not otherwise preclude approval under an ANDA
- Comparative analyses can assist applicants in identifying differences in the user interface and in determining whether additional data (e.g., comparative use human factors studies) should be submitted

User Interface

- Certain labeling differences that flow from permissible differences in design of a proposed combination product may be permissible and will be evaluated on a case-by-case basis
- FDA intends to assess whether an end-user can use the generic combination product when it is substituted for the RLD without the intervention of the health care provider and/or without additional training prior to use of the generic combination product
- Engage early during product development via controlled correspondence and pre-ANDA processes

Generic Drug User Fee Amendments (GDUFA II)

- GDUFA (GDUFA II) was reauthorized on August 18, 2017 to facilitate timely access to high quality, affordable generic medicines
- In accordance with the GDUFA II Commitment Letter that accompanied the legislation, FDA committed to developing a pre-ANDA program to assist applicants of complex products

1. Food and Drug Administration Reauthorization Act of 2017 (Public Law 115-52)
2. https://www.fda.gov/media/101052/download

GDUFA II Commitment Letter

Complex Product – generally includes:

1. Products with complex active ingredients (e.g., peptides, polymeric compounds, complex mixtures of APIs, naturally sourced ingredients); complex formulations (e.g., liposomes, colloids); complex routes of delivery (e.g., locally acting drugs such as dermatological products and complex ophthalmological products and otic dosage forms that are formulated as suspensions, emulsions or gels) or complex dosage forms (e.g., transdermals, metered dose inhalers, extended release injectables)
2. **Complex drug-device combination products (e.g., auto injectors, metered dose inhalers)**; and
3. Other products where complexity or uncertainty concerning the approval pathway or possible alternative approach would benefit from early scientific engagement.

Complex Drug-Device Combination Products

- Examples include
  - Auto injectors
  - Metered dose inhalers
  - Soft mist inhalers
  - Metered nasal spray products
  - Dry powder inhalers


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