Device Considerations for Pre-ANDA Meeting Requests for Complex Drug-Device Combination Products

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Session: Drug-Device Combination Products from the Device Perspective

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Outline

- General overview of combination products
- Regulatory considerations for drug-device combination products submitted in abbreviated new drug applications (ANDAs)
- Pre-ANDA meetings for complex generic products
  - Complex drug-device combination products
  - Product development (PDEV) vs. Pre-submission (PSUB) meetings
  - Common types of requests received in PDEV pre-ANDA meetings
- Considerations for device-related questions
  - User interface vs. performance characteristics
- Conclusions

What is a Combination Product?

- A “combination product” is:
  - A product comprised of two or more different types of medical products (e.g., drug and device, drug and biological product, device and biological product, or all three together).

Types of Combination Products

	"Single-entity"	"Co-packaged"
Description	Chemically or physically combined constituent parts	Constituent parts packaged together
Examples	• Drug-eluting stent • Prefilled syringe • Transdermal patch • Bone void fillers with drugs	• First-aid or surgical kit • Syringe packaged with vial of drug • Drug + prefilled diluent, reconstitution/ transfer device, fillable cartridge and wearable patch
Reference	21 CFR 3.2(e)(1)	21 CFR 3.2(e)(2)

- There is another type of combination product, which includes constituent parts that are packaged separately, but specifically labeled for use with one another to achieve the intended therapeutic effect.

Primary Mode of Action

- Combination products have multiple "modes of action" (see 21 CFR 3.2(k))
- There are three potential modes of action for a combination product:
  - Drug
  - Device
  - Biological product
- Combination products are assigned to a "Lead Center" having primary responsibility for their review
  - Will consult with non-Lead Center via Inter-Center Consult process, where appropriate
- Lead Center is based on:
  - The "primary mode of action" (PMOA): Constituent part that provides the greatest contribution to the product's intended therapeutic effects

Drug-Device Combination Products













General Framework for ANDAs

- Approval of generic drug starts with a listed drug – generally an innovator product 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).
- In the context of drug-device combination products, applicants should generally seek approval of a presentation approved for the RLD (e.g., autoinjector).

Generic Drug Product Substitutability

In relation to the RLD, generic drug 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.

General Principles

Considerations include, but are not limited to:

- **Performance characteristics**
  - Review of a generic drug-device combination product is informed by the general framework for ANDAs, but also takes into consideration the performance of the device constituent and its interaction and impact on the delivery of the drug constituent.
- **User Interface**
  - Generic and RLD do not need to be identical, as long as differences do not preclude approval under an ANDA.
  - FDA expects that end-users 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.

Complex Drug-Device Combination Products

- As defined in the GDUFA II Commitment Letter, complex products are:
  - Products with complex active ingredients, complex formulations, complex routes of administration, or complex dosage forms;
  - **Complex drug-device combination products**; and
  - Other products where complexity or uncertainty concerning the approval pathway or possible alternative approach would benefit from early scientific engagement.
- Examples of a **complex drug-device combination product:**
  - Prefilled auto-injectors
  - Metered-dose inhalers, dry powder inhalers
  - Transdermal and topical delivery systems
- Examples of a **non-complex drug-device combination product:**
  - Dosing cups and syringes for oral liquid formulations

Guidance for Industry: Formal meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA (Oct 2017): https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm578366.pdf

Types of Pre-ANDA Meetings for Complex Products

- Product Development (PDEV)
  - Provide for discussion of specific scientific issues or questions (e.g., a proposed study design, alternative approach, or additional study expectations), in which FDA will provide targeted advice regarding an ongoing ANDA development program.
- Pre-Submission (PSUB)
  - Provide an opportunity for prospective ANDA applicants to discuss and explain the format and content of the ANDA to be submitted (e.g., data to support equivalence claims, types of data that will be contained in the ANDA).

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Common Types of Requests Received in PDEV Pre-ANDA Meetings

- There is a Product-Specific Guidance (PSG)
  - Evaluation of proposed alternative approach for bioequivalence
  - Evaluation of proposed study design that deviates from the PSG
  - Multiple questions or complex issues not covered by the PSG
- There is not a PSG
  - Evaluation of proposed approach for bioequivalence

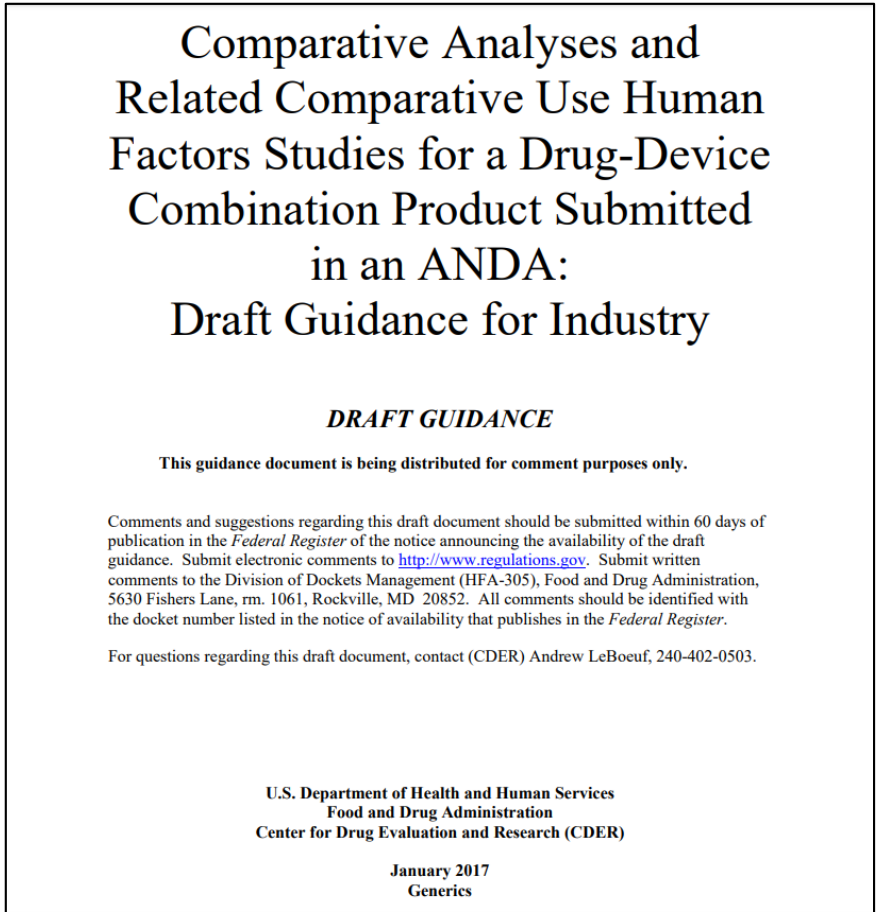
Any type of request can include device-related questions

Proposed Test Device (User Interface)

- FDA assessment:
  - Comparative (threshold) analyses as per the FDA guidance, *Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA* (Jan 2017)
    - Labeling comparison
    - Comparative task analysis
    - Physical comparison of the delivery device constituent part
- Information to submit:
  - Samples of Test and RLD devices
  - Comparative (threshold) analyses per guidance above
  - Specific question(s) based on the outcomes of comparative analyses

Note: *Device (user interface) questions may be submitted as standard Controlled Correspondence (CC) which has a 60-day clock, but it may be converted to complex CC (120-day clock).*

Draft Guidance: Comparative Analyses



Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA: Draft Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Andrew LeBoeuf, 240-402-0503.

U.S. Department of Health and Human Services
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Generics

Assessment of Identified Differences

Consider any identified differences between the user interface of a proposed generic combination product and its RLD in the context of the *overall risk profile* of the product

- **No Differences**
- **Minor Differences**
  - Do not affect an external critical design attribute
- **Other Differences**
  - *May* impact an external critical design attribute that involves administration of the product
  - Prospective applicants should consider re-design to minimize differences from the RLD
  - Potential need for additional information and/or data beyond the comparative analyses (e.g., in vivo or in vitro data, or comparative use human factors studies) to support the ANDA submission

Recommendations

- Read the draft guidance for industry on *Comparative Analyses.*
- Consider user interface and critical tasks of the RLD product and evaluate risks associated with any identified differences in user interface.
- Perform comparative analyses throughout development and seek to minimize differences from RLD.
- Consider any differences in terms of the risk of impacting an external critical design attribute that involves administration of the product.
- Communicate early and often with FDA:
  - Controlled correspondences
  - Pre-ANDA meeting requests for complex products

Proposed Test Device (Performance)

- FDA assessment:
  - Bioequivalence (BE) perspective → PSGs (Test vs. Reference)
  - Drug Product Quality (DPQ) perspective → General guidances for industry

- Information to submit in the pre-ANDA meeting package:
  - Proposed study plans supported by scientific rationale, clear and concise justification, preliminary data (if available) and/or literature.
  - Specific question(s) related to design/engineering and performance/ functionality aspects for the proposed Test device constituent (BE and DPQ, as applicable) *clearly separated from user interface questions*.

Conclusions

- Development of device constituent in generic drug-device combination products is challenging
  - Substitutability for its RLD
  - Performance testing (BE and/or drug product quality aspects)
- PDEV pre-ANDA meeting requests for complex products is one mechanism to communicate early and often with FDA
  - Focus on complex situations or issues for the development program
  - Clearly defined proposals and questions
  - Supported by scientific rationale, clear and concise justification
  - Supported by preliminary data (if available) and/or literature

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