U.S. FOOD & DRUG ADMINISTRATION

Pre-ANDA Evaluation of Drug Delivery Device Constituents

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Generic Drug Product Substitutability

In relation to the reference listed drug (RLD), generic products are expected to be:

- **Pharmaceutically Equivalent**

  The same active ingredient, dosage form, strength, route of administration and meet the same 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 (e) defines a combination product as composed of any combination of:

- a drug and a device;
- a biological product and a device;
- a drug and a biological product; or
- a drug, device, and a biological product.

Classifications of Combination Products

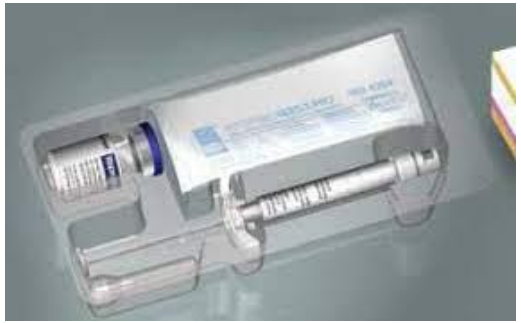
Per the Office of Combination Products:

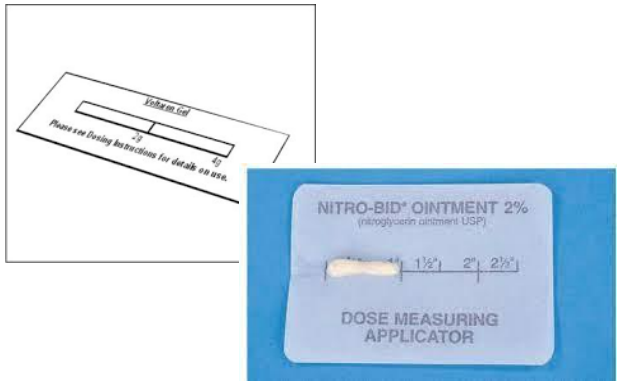
- There are 9 types of combination products
- **Types 1, 2, 4, and 7** relate to drug-containing combination products are the most common types for generics

www.fda.gov/media/80384/download
www.fda.gov/combination-products/about-combination-products/combination-product-definition-combination-product-types

Type 1 Combination Products:

Convenience Kit or Co-Packaged Product





Type 2 Combination Products:

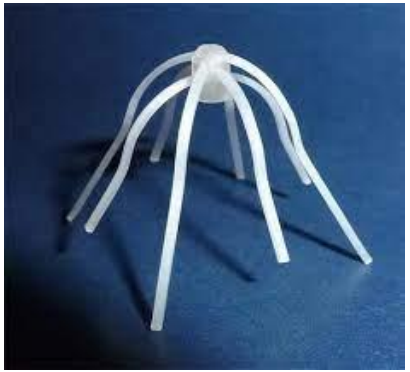
Pre-filled Drug Delivery Device/Systems

- Sole purpose of the device is to deliver drug

Type 4 Combination Products:

Device Coated/Impregnated/Otherwise combined with drug

– Device has additional function (and delivers drug)



Type 7 Combination Product

Separate Products Requiring Cross-Labeling

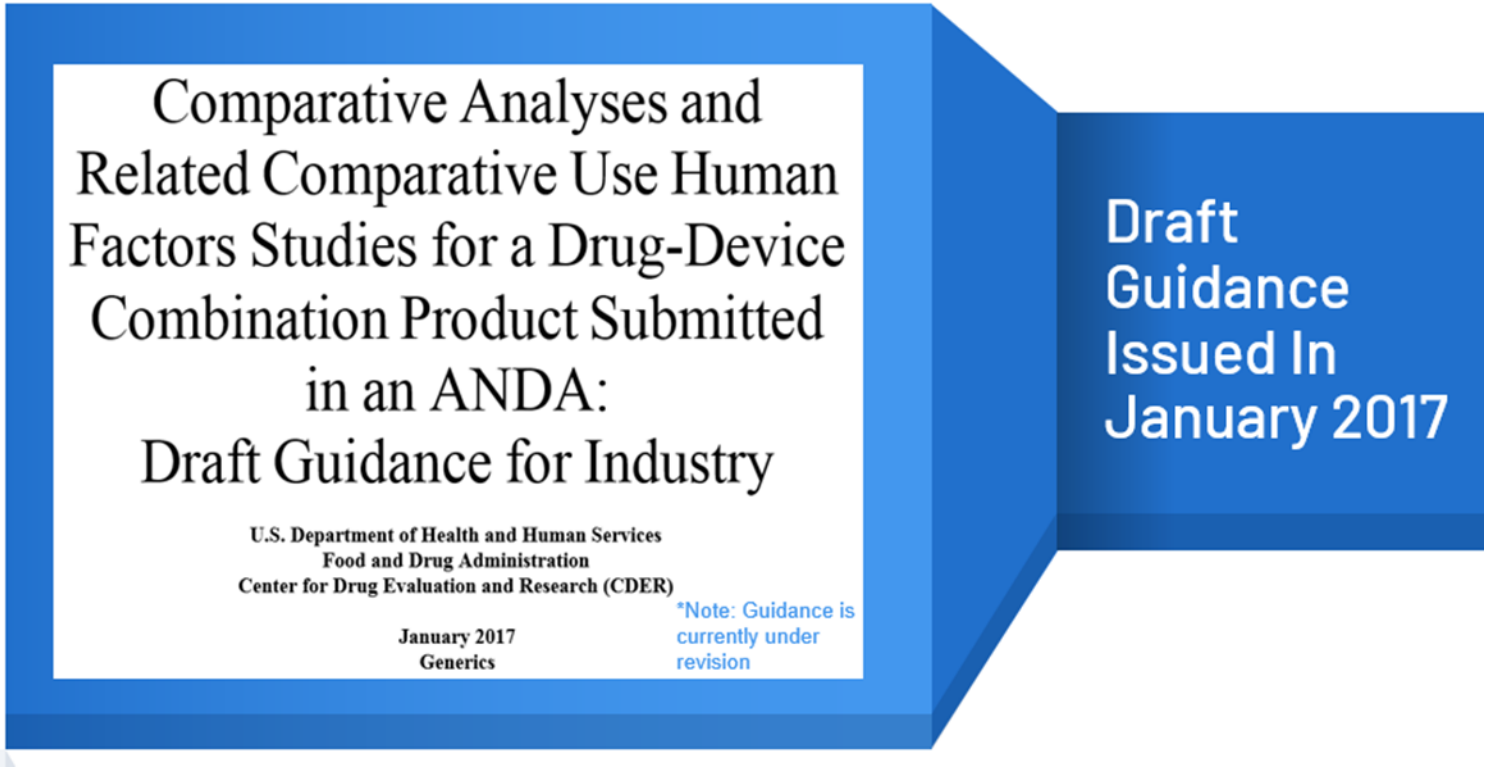
– Example: light-activated drugs that are not co-packaged but labeled for use with a specific device

General Principles for Combination Products

Considerations include, but are not limited to:

- Performance characteristics
  - Takes into consideration the performance of the device constituent and its interaction and impact on drug delivery
  - Not the focus of the Comparative Analyses
- User Interface
  - Focus of review and evaluation in a comparative analyses

Comparative Analyses Guidance



https://www.fda.gov/media/102349/download

Key Points From Draft Guidance

- The RLD does no need to be identical
- Differences in the design of the user interface should be adequately analyzed, scientifically justified, and not otherwise preclude approval under an ANDA
- Design differences in the design of the user interface should be minimized in early phases of drug development
- Certain labeling differences may be allowed (on a case-by-case basis)
- FDA expects that end users can use the generic combination product when it is substituted for the RLD without interventions of the health care provider and/or without additional training prior to use

https://www.fda.gov/media/102349/download

Key Points From Draft Guidance

- Baseline assessment for any identified differences occurs during comparative analyses
- Will determine whether additional information and/or data is warranted
  - May include Comparative Use Human Factors Studies
  - Not intended to demonstrate the safety or effectiveness of the proposed generic combination product

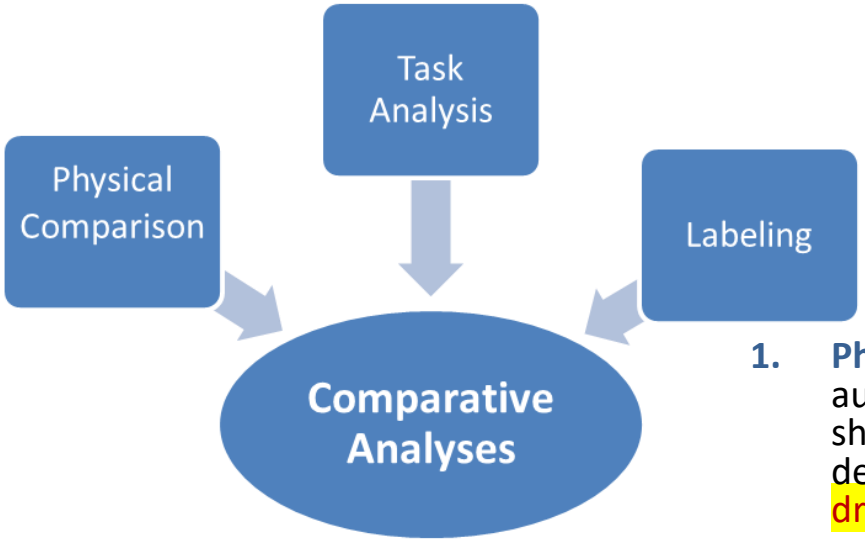
Definitions

- **User Interface:** all components of a product with which a user interacts,
  - labeling and packaging,
  - the device delivery constituent part,
  - any associated controls and displays

- **External Critical Design Attributes:** Those features that directly affect how users perform a critical task that is necessary to use or administer the drug product

- **Critical Tasks:** 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

Comparative Analyses (CA)



1. **Physical Comparison of Device Constituent Parts:** Visual, auditory, tactile examination of the physical features (size, shape, feedback) of the RLD, compared to those of the delivery device constituent part of the proposed generic drug-device combination product
2. **Comparative Task Analysis:** Comparative task analysis is assessed between the RLD and the proposed generic drug-device combination product
3. **Labeling Comparison:** Side-by-side, line-by-line comparison of the full prescribing information, instructions for use, and descriptions of the delivery device constituent parts of the generic drug-device combination product and its RLD

CA: Outcomes of Comparisons

In the context of the *overall risk profile* of each comparison made between the proposed generic and RLD, user interfaces should be assigned one of the following outcomes:

- **No Difference**
- **Minor Difference**
  - A difference in the proposed generic user interface, in comparison to the RLD user interface, that does not affect an external critical design attribute
- **Other than Minor Difference**
  - A difference in the proposed generic user interface, as compared to the RLD user interface that ***may*** impact an external critical design attribute that involves administration of the product

CA: Pre-ANDA Assessment Outcomes

- Complete vs. incomplete
- If incomplete, may involve one or more of the individual analyses.
- Common omissions and errors include (but are not limited to):
  - Missing comparative measurements or images
  - Omitted tasks
  - Omitted comparison outcomes (no, minor, or other difference) or justification of differences
  - Missing sections of the IFU
  - Text changes in labeling that do not stem from permissible differences in user interface designs.

CA: Examples of Common Omissions

Physical Comparison	Comparative Task Analysis	Labeling Comparison (IFU for Pre-ANDA)
No dimensions provided on comparative images	Use of the IFU comparison as a substitute for identifying the critical tasks	Images don't accurately depict the proposed product
Differences identified but not categorized as recommended in the Guidance	Not linking an identified physical difference to performance of a specific task	Certain sections are omitted such as any preparation and cleaning steps
Minor or other differences identified but not justified	URRA submitted instead of Comparative Task Analysis	Changes in text that may not be permissible

URRA vs. Comparative Analyses

Table 1. Example Row URRA for Formative Evaluation

Task	Potential use error(s)	Potential Hazard/Hazardous Situation	Potential harm	Severity of potential harm	Risk control measures	Critical task (Yes/No)
Remove cap	User twists cap while removing it	Clogged needle/no medication will flow.	Potential reduction of efficacy / worsening of symptoms.	Serious	Statements under "Remove cap" step in instructions stating: • "Remove the cap by pulling it straight off," and • "Do not twist the cap."	Yes
		Clogged needle/no medication will flow.	Potential reduction of efficacy / worsening of symptoms.	Serious		
		Foreign body/injection of foreign body.	Infection (injection of needle shield fragment).	Serious		

A threshold analysis should include the following human factors analyses:		
1	**Labeling comparison**	Side-by-side, line-by-line comparison between the proposed product and the product it references that includes • full prescribing information, • instructions for use, • container labels and carton labeling, and • descriptions of the products
2	**Comparative task analysis**	A comparative task analysis of the proposed product and the product it references (comparator)
3	**Physical comparison of device UIs**	Examine, through a visual or tactile examination, the physical features of the product that it plans to reference and compare them to those of the proposed product

Key Takeaways

- A Complete CA includes:
  - A **physical comparison** of the proposed generic and RLD device user interfaces (including measurements).
  - A **comparative task analysis** that includes all tasks needed to correctly administer the drug (including prep steps and cleaning).
  - A **labeling comparison**. During pre-ANDA assessment, the focus is on the IFU. During ANDA review, all labeling components are evaluated.

- Pre-ANDA assessment of CA can provide feedback about:
  - Whether a proposed device may be appropriate for an ANDA submission.
  - Whether there may be "other than minor differences" between the user interfaces that may warrant submission of additional data to the ANDA to support that the differences won't alter the overall risk profile of the proposed generic product, as compared to the RLD.

- Generic product labeling should be the same as that of the RLD, although some differences are permissible as described at 21 CFR 314.94(a)(8)(iv).

Recommendations

1. Read and understand the draft guidance for industry, *Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA*.

2. Throughout drug-device combination product development,
   - Consider user interface and critical tasks of the RLD product
   - Evaluate risks associated with each identified difference between the proposed generic and RLD user interfaces
   - Perform iterative comparative analyses and seek to minimize differences from the RLD.

https://www.fda.gov/media/102349/download

Recommendations (cont.)

3. Consider user interface differences in terms of whether they may impact an external critical design attribute that involves product administration.

4. If your device design is final, then consider whether additional data (beyond the CA) are needed to support/justify any remaining user interface differences (e.g., a Comparative Use Human Factors study or other in vivo or in vitro study).

5. Talk early and often with FDA through:
   - controlled correspondences
   - pre-ANDA meeting requests for complex products.

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