# Disclaimer

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# Generic Drug-Device Combination Product Assessment

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# Drug-Device Combination Product

- Therapeutic and diagnostic products that combine drugs, devices, and/or biological products.
- Combination products are defined in 21 CFR 3.2(e)
  - Drug-device combination product contains a drug constituent part and device constituent part(s)
- Center for Drug Evaluation and Research (CDER) regulates when drug product is primary mode of action.
- Drug and device constituent parts may be integrated, co-packaged, or cross-labeled.

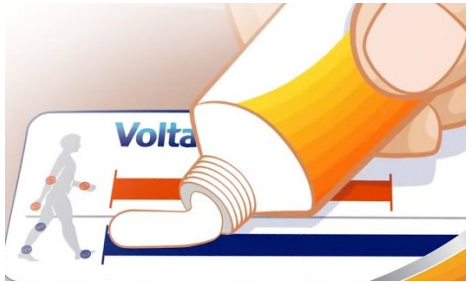
For questions regarding combination product types, contact the Office of Combination Products: combination@fda.gov

https://www.fda.gov/combination-products

# Common Examples of Drug-Device Combination Products

Co-Packaged Products

- Drug and device are provided as individual constituent parts within the same package.
- Example: Drug product is packaged with device(s) or accessory kits (e.g., empty syringes, dosing cards, safety needles).


# Common Examples of Drug-Device Combination Products

Pre-filled Drug Delivery Device

- Drug is filled into or combined with the device and the sole purpose of the device is to deliver drug.
- Examples: Prefilled drug syringe, auto-injectors, metered-dose inhalers, dry powder inhalers, nasal-spray, pumps, transdermal systems.
- Pre-filled drug delivery device may be co-packaged with injection needles.






# Other Types of Drug-Device Combination Products

Device Coated or Impregnated with Drug

- Device has an additional function in addition to delivering the drug.
- Example: Drug-eluting implant or vaginal ring.
- May also contain co-packaged devices such as delivery system.

Cross Labeled Combination Products

- Example: Prefilled syringe used with light source device supplied separately.



# General Principles for Generic Drug-Device Combination Products

- Generic drug-device combination products classified as therapeutically equivalent to the reference listed drug (RLD) can be expected to produce the same clinical effect and safety profile as the RLD under the conditions specified in labeling.
- Additional information necessary to support approval of generic combination product include:
  - Performance characteristics (while not BE, device constituent quality is important):
    - Takes into consideration the performance of the device constituent and its interaction and impact on drug delivery
    - Extractables/leachable studies, performance testing, stability studies
  - User Interface:
    - Includes all components of the product with which a user interacts

# Comparative Analysis

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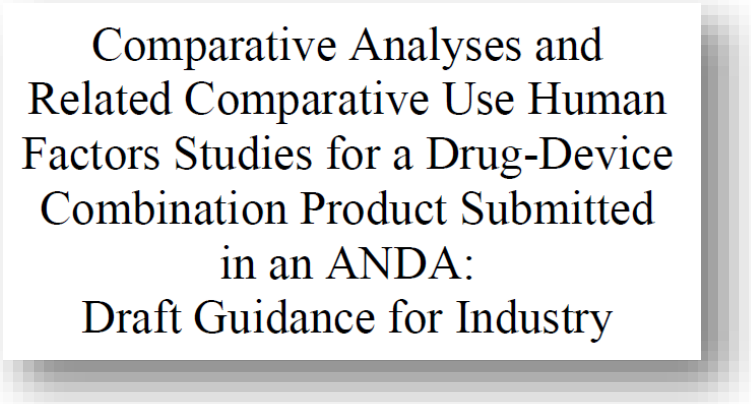
# Generic Combination Product Substitutability

- User Interface includes all components of the product with which a user interacts:
  - Delivery device constituent of combination product.
  - Any associated controls and displays.
  - Product labeling and packaging.




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

# Key Points from Comparative Analyses Guidance

- The generic device design does not need to be identical to the RLD.
- 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).

# Key Points from Comparative Analyses Guidance

- FDA expects that end users can use the generic combination product when it is substituted for the RLD without intervention of the health care provider and/or without additional training prior to use.
- Similarity of proposed generic and RLD device user interfaces evaluated through comparative analyses.
- Will determine whether additional information and/or data is warranted to demonstrate substitutability.

# Context of Use Considerations for Assessing Differences

- Urgency of Use: Emergency vs. Non-Emergency
- Frequency of Use: Single use vs. Repeated use
- End-Users: Patient and caregiver groups vs. healthcare providers
- Environment of Use:
  - Clinical: Hospital, outpatient clinic
  - Nonclinical: home, school, etc.
- Patient Population:
  - Dexterity (i.e., Range of motion, Fine motor coordination)
  - Incapacitated (naloxone)
  - Adults, pediatrics
- Consider these factors for all tasks (e.g., priming, cleaning procedures, storage).

# Conducting Comparative Analyses

- Potential applicants should examine, among other things, the external critical design attributes of the proposed delivery device constituent part in comparison to the external critical design attributes of the RLD.
- Three types of comparative analyses (physical comparison, comparative task analysis and labeling comparison) can be used throughout the generic development program for the purposes of identifying, evaluating, and minimizing design differences.

External Critical Design Attributes
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.

# Physical Comparison

- Visual, auditory, tactile examination of the physical features of the proposed generic to the RLD.
  - Size, shape, color/transparency, feedback, texture, sound, thickness, font size/shape
  - Include all components necessary to delivery drug (e.g., packaging, connectors)
- External design mechanisms and features.
- Include samples and side-by-side clear, detailed, and color photographs.
- Clearly identify, characterize, and provide justification for differences noted.

# Comparative Task Analysis

- Analyze and compare step-by-step use processes
  - Identify steps that end-users need to perform to use the product
    - From opening the packaging to disposing of the product (e.g., disposing of transdermal products)
- Highlight differences in tasks that arise due to difference in user interface design. Note if differences may impact an existing critical task or give rise to a new critical task.
- Clearly identify, characterize, and provide justification for differences noted.
- Task comparison should be focused on tasks rather than labeling.

# Labeling Comparison

- For Pre-ANDA device evaluations:
  - Focuses on the instructions for use (IFU).
- For the ANDA:
  - Side-by-side, line-by-line, figure-by-figure comparison of all labeling components
  - Emphasis on those sections of the labeling that describe the use of the drug-device combination product
- Generic product labeling should be the same as that of the RLD, except for permissible differences described at 21 CFR 314.94(a)(8)(iv).
  - Labeling differences that stem from permissible differences in design between the user interface for the proposed generic combination product and its RLD may fall within the scope of permissible differences in labeling for a product approved under an ANDA.

# Outcomes from Comparative Analyses

- Each comparison has an outcome:
  - No Difference
  - Minor Design Difference:
    - If the difference 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
  - Other Design Difference:
    - If any aspect of the comparative analyses suggests that difference in the design of the user interface of a proposed combination product as compared to the RLD *may* impact an external critical design attribute that involves administration of the product
- Consider any identified differences and the context of use when evaluating the overall risk profile of the product.

# Minor Design Differences

- Design difference will not affect an external critical design attribute.
- Likely to be viewed as acceptable provided data and information submitted by applicant demonstrate the difference is minor.
- Assessed on an ANDA-specific basis.
- Example:
  - Different color of the plunger rod for a prefilled syringe, and the color of the plunger rod is not critical to the correct use of the device.

# Other Design Differences

- Difference in design of user interface of generic as compared to RLD may impact an external critical design attribute that involves use of the product.
- A product with an “other” design difference may be approved as an ANDA but may require further evaluation.
- Assessed on an ANDA-specific basis.

# Options to Address “Other” Design Differences

When other design differences are identified:

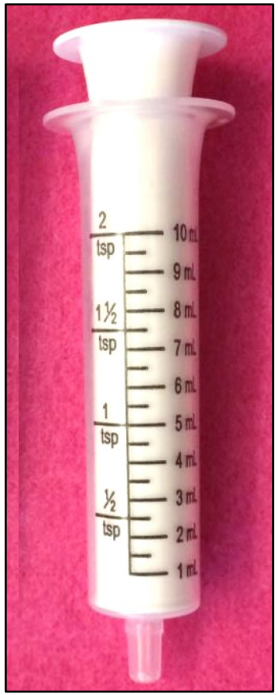
- Consider modifying design of user interface to minimize differences
  - Comparative human factors-based risk evaluations should be part of the iterative drug-device combination product development process.
- Provide additional data/information such as:
  - A comparative use human factors (CUHF) study , an in vitro study, or published literature.
  - Type of information/data will depend on the differences and risks being considered.
  - Information should support/justify that the difference will not alter overall risk profile when generic substitution occurs.
  - Recommend to contact FDA via Pre-ANDA communication meeting prior to conducting CUHF study.

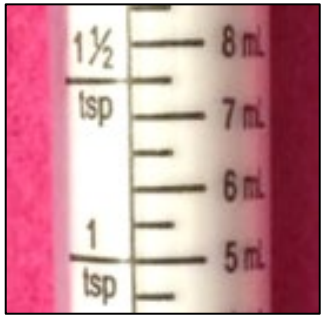
# Suggestions from an FDA Assessor

# Oral Combination Products

- Examples: co-packaged dosing cups, oral syringes, and oral droppers
- Consider minimizing differences from RLD in dispensing devices
  - Remove extraneous markings (measurements)
  - Ensure correct orientation of markings
  - Ensure dispensing device can measure exact dose(s) that are recommended in labeling
  - Ensure adequate contrast between the drug product and dispensing device

# Extraneous Markings




Note: Syringe contains measurement markings that are not referred to in the RLD's labeled dosage directions

*Depictions are hypothetical and for illustrative purposes only

# Additional Guidances

- Guidance for Industry: Safety Considerations for Product Design to Minimize Medication Errors (April 2016)*
- Guidance for Industry: Dosage Delivery Devices for Orally Ingested OTC Liquid Drug Products (May 2011)*

* FDA updates guidance periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

# Injectable Combination Products

- Examples: prefilled syringes, injection kits, and autoinjectors
- Consider context of use, end-users, environments of use, patient population
- Consider the differences from the RLD for each device constituent
  - Needles, safety devices, connectors

# Common Deficiencies for Injectable Combination Products

- Labeling – Instructions for Use does not accurately represent proposed product
- Images in labeling do not accurately represent proposed product
- Dose/measurement markings do not correspond to dose recommended in prescribing information

# Summary

- All design differences should be identified, adequately analyzed, and scientifically justified
- Context of use should be considered when assessing differences as minor versus other design differences
- If an “other” design difference is present, recommend discussing early with FDA in a controlled correspondence or pre-ANDA meeting
  - Include your proposal of additional information or data to assess the acceptability of differences identified in the user interface
  - Submit specific questions with your proposal

# BE Recommendations for Complex Generic Drug-Device Combination Products - Orally Inhaled Drugs and Auto-Injectors

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Division of Bioequivalence III
Office of Bioequivalence
Office of Generic Drugs

AAM GRx + Biosims 2023 – October 2

# PSG Recommendations for Epinephrine Autoinjectors

| Parameter | Epinephrine Autoinjectors (Draft Guidance Recommended in 2016) |
|---|---|
| **Formulation** | Test (T) and reference (R) formulations should be qualitatively (Q1) and quantitatively (Q2) the same |
| **Device Considerations** | Prospective applicants examine the size and shape, external critical design attributes, and external operating principles of the RLD devices when designing the test devices |
| **In Vitro Studies** | Delivered volume<br>Ejection time<br>Trigger force<br>Extended needle length } Population Bioequivalence (PBE) analysis<br>Needle integrity post-injection: qualitative comparison between T and R devices regarding the ability to trigger the injection at the angle of incidence, the needle's capability to penetrate the material, and the integrity of the needle post-injection |

Product specific guidance (PSG) link:
*https://www.accessdata.fda.gov/drugsatfda_docs/psg/Epinephrine_intramuscular%20injection_RLD%2019430_RC12-16.pdf*

# PSG Recommendations for Sumatriptan Succinate Autoinjectors

| Parameter | Sumatriptan Succinate Autoinjectors |
|---|---|
| **Formulation** | T and R formulations should be Q1 and Q2 the same |
| **Device Considerations** | Prospective applicants examine the size and shape, external critical design attributes, and external operating principles of the RLD devices when designing the test devices |
| **In Vitro Studies** | Delivered volume<br>Extended needle length } PBE analysis<br><br><u>Supportive characterization studies</u><br>Ejection time<br>Trigger force |

PSG link:
*https://www.accessdata.fda.gov/drugsatfda_docs/psg/PSG_020080-Autoinj.pdf*

Recommendation for test batches: final device constituent part and final drug constituent formulation intended to be marketed

# PSG Recommendations for Fluticasone Propionate and Salmeterol Xinafoate Dry Powder Inhaler (DPI)


| Parameters | Fluticasone Propionate and Salmeterol Xinafoate DPI |
|---|---|
| Formulation | T and R formulations should be Q1 and Q2 the same |
| Device Consideration | Consider the following characteristics of R when designing the T product: passive device, size and shape of the R product, number of doses in the R product, external critical design attributes of the R product and dose counter |
| In Vivo PK Study | Fasting study on all strengths |
| Comparative Clinical Endpoint Study | Comparative clinical endpoint study on the lowest strength |
| In Vitro Studies | Single Actuation Content (SAC)<br>Aerodynamic Particle Size Distribution (APSD) |

PSG link: *https://www.accessdata.fda.gov/drugsatfda_docs/psg/PSG_208799.pdf*

# PSG Recommendations for Albuterol Sulfate Metered Dose Inhaler (MDI)


| Parameters | Albuterol Sulfate MDI |
|---|---|
| Formulation | T and R formulations should be Q1 and Q2 the same |
| Device Consideration | Consider the following characteristics of the R when designing the T product: size and shape of the R product, number of doses in the R product, external operating principles and external criterial design attributes of the R product and dose counter |
| In Vivo PK Study | Fasting study |
| Pharmacodynamic Study | Bronchoprovocation Study |
| In Vitro Studies | SAC, APSD, Spray Pattern, Plume Geometry, Priming and Repriming |

PSG link: *https://www.accessdata.fda.gov/drugsatfda_docs/psg/PSG_020503.pdf*

# Test Device Changed After Completing BE Studies in the ANDA Submission for Orally Inhaled Drug Products

- **Issue**: None of the test batches in the studies represent the final to-be-market product/device. How to bridge current data to the product to be marketed?

- **Recommendation**: Provide evidence supporting that device modifications do not impact product performance and study outcome
  - Typically, in vitro BE bridging studies are recommended.
  - For in vitro BE bridging studies: use at least 3 batches of post-change product vs. at least 3 batches of unexpired RLD product, with no fewer than 10 units from each batch
  - Depending on the type and number of changes: additional BE bridging studies (e.g., in vivo) might be required.

# Tips for Submitting Bridging Studies in an ANDA for Orally Inhaled Drug Products

- Specify changes
  - Between the test product used in each in vitro and in vivo BE study and the to-be-marketed product
  - Describe all changes in detail, irrespective of the degree of the changes

- Bridging study justifications:
  - Explain why bridging studies were conducted to support the modifications

- No bridging studies??
  - Outline the rationale why bridging studies are not necessary

# Incorporate a Dose Counter for a Test Product After Completing BE Studies for Orally Inhaled Drug Products

- **Issue:** the applicant proposed to incorporate a dose counter after all of the BE studies were conducted comparing the test product without a dose counter to the reference product that had a dose counter.

- **Recommendation:**
  - In vitro BE studies (e.g., SAC, APSD, spray pattern, plume geometry, and priming and repriming for MDI products) comparing the post-change test product with a dose counter to the reference product with a dose counter

# Summary and Suggestions

- Orally inhaled and auto-injector drug products are drug-device combination products
- A drug device design can impact the in vitro and in vivo performance, as well as drug delivery
- BE studies should be conducted with the to-be-marketed device
- If the device is re-designed late after the completed BE studies, it may affect in vitro characterization. Bridging data may be needed between device versions.
- There are multiple channels to communicate with the FDA, including controlled correspondences, product-development meetings, mid-cycle review meetings, post-complete response letter meetings. All of them serve to address the industry's questions at various stages of generic drug development and regulatory approval.

# Current and Future Opportunities

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Director, Division of Therapeutic Performance, ORS, OGD, CDER

# Pre-ANDA Program

- Goal is to clarify regulatory expectations for prospective applicants early in product development, assist applicants in developing more complete submissions, promote a more efficient and effective ANDA assessment process, and reduce the number of assessment cycles required to obtain ANDA approval.
- Some elements are tailored to enhance development of complex generic products.
- https://www.fda.gov/drugs/generic-drugs/pre-anda-program

# Development of Complex Generic Products

- Complex generic products can raise unique scientific and regulatory considerations.
- These generally include:
  - Products with complex active ingredients, complex formulations, complex routes of delivery, complex dosage forms.
  - Complex drug-device combination products.
- GDUFA III Commitment letter: https://www.fda.gov/media/153631/download?attachment
- MAPP 5240.10: https://www.fda.gov/media/157675/download

# Complex Drug-Device Combination Products

A complex drug-device combination product includes:

- Drug constituent part is contained within or co-packaged with a product-specific device constituent part in which device design may impact drug delivery to site of action and/or absorption (e.g., device design meters dose).
- User interface may have specific use considerations (e.g., when product label indicates users should be trained by healthcare provider).

Complex combination products generally include:

- Multi-dose pen injectors, pre-filled autoinjectors
- Metered-dose inhalers, dry powder inhalers
- Metered-dose pumps for topical/transdermal formulations
- Intrauterine systems

Simple combination products generally include:

- Oral dosing cups, simple pre-filled syringe, dosing cards for topical ointments

# Product-Specific Guidances for Generic Drug Development

- Product-specific guidances (PSGs) are published by FDA.
- Describes Agency's current thinking and expectations on how to develop generic drug products that are therapeutically equivalent to the RLD.
  - https://www.accessdata.fda.gov/scripts/cder/psg/index.cfm
- Device recommendations describes device constituent part and provides recommendations to industry for RLD device characteristics to examine during generic development.

Etonogestrel Implant, NDA 021529, PSG

**Additional information:**

Device:
The reference listed drug (RLD) product is presented as a removable implant in a disposable applicator. The implant and the applicator are device constituents used to administer the drug.

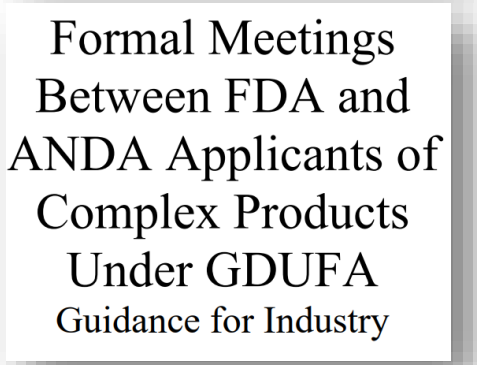
FDA recommends that prospective applicants examine the size and shape, external critical design attributes, and external operating principles of the RLD devices when designing the test devices including the following characteristics:

- Radiopaque implant
- Preloaded, single-use applicator
- Gauge and length of applicator needle

User Interface Assessment:
An ANDA for this product should include complete comparative analyses so FDA can determine whether any differences in design for the user interface of the proposed generic product, as compared to the RLD, are acceptable and whether the product can be expected to have the same clinical effect and safety profile as the RLD when administered to patients under the conditions specified in the labeling. For additional information, refer to the most recent version of the FDA guidance for industry on *Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA.*[a]

# Pre-ANDA Feedback on Device User Interface

- Potential applicants are encouraged to submit comparative analyses to FDA for review in Pre-ANDA Program.
- Controlled Correspondences https://www.fda.gov/media/164111/download
- Product Development Meetings https://www.fda.gov/media/107626/download

# User Interface Related Questions

- Submissions should include:
  - Comparative analyses
  - Specific question about user interface (questions related to quality should be submitted in a separate controlled correspondence)
  - Three samples of proposed generic and RLD
    - If samples are prototypes, the correspondence should specify as such and identify any components (including device labeling) that have been omitted or are still in development
- Comparative Use Human Factors (CUHF) study protocols may be submitted in either Pre-ANDA Product Development Meetings or Controlled Correspondences for review.

# GDUFA Science and Research Program

- Grant and contract research is ongoing to support generic drug-device combination product development
- Research areas include:
  - Patient perceptions on generic drug-device combination product substitution.
  - Categorization of differences in the design of the user interface.
  - Exploration of in vitro or in vivo approaches to assess “other design differences” as alternatives to comparative use human factors (CUHF) studies.
- Future research may include conduct of FDA-designed CUHF studies to evaluate certain types of differences and impacts on user error rates.

GDUFA Science and Research Reports: https://www.fda.gov/drugs/generic-drugs/generic-drug-research-related-guidances-reports

# Opportunities for Discussion

- As new draft FDA guidances for industry are published, we encourage comments and industry dialogue.
- FDA CDER Small Business & Industry Assistance Events: Advancing Generic Drug Development:
  Translating Science to Approval https://sbiaevents.com/
- Center for Research on Complex Generics
  https://www.complexgenerics.org/events/
  - May 10, 2023: Drug-Device Combination Products 101: Identifying, Developing, and Evaluating Drug-Device Combination Products
  - Spring 2024: Drug-Device Combination Products: Updates and Challenges in Demonstrating Generic Substitutability

# We Are OGD

***Ask me why...***

"I make sure that the **generic** drug and the **brand** drug work **the same**."

"The first time I was able to buy my son's inhaler as a generic and realized that my out of pocket dropped, I cried and was able to breathe a sigh of relief."

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