Device and User Interface Assessment Recommendations in Drug-Device Combination Product PSGs

Karthika Natarajan
Staff Fellow,
DTP-1 | ORS | OGD
CDER | U.S. FDA

Facilitating Generic Drug Product Availability through Product-Specific Guidances (PSGs) – April 25, 2024

Drug-Device Combination Products

Combination Products

A combination product (21 CFR 3.2) is a product composed of any combination of the following

- 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

Drug-Device Combination Products (DDCPs) and Regulatory "Home"

- Combination product comprising a drug constituent part and a device constituent part
- Can have either a drug or device primary mode of action (contributes most to the intended therapeutic effect or action)
- CDER regulates DDCPs where the drug provides the primary mode of action (PMOA)

Today's focus

Drug-Device Combination Products (DDCPs) with Drug PMOA

- A DDCP has a drug PMOA if it:
  - Meets the definition of drug contained in section 201(g)(1) of the FD&C Act and
  - Does not have a biological product or device mode of action
- Can be a single-entity, co-packaged or cross-labeled drug-device combination product

Types of Drug-Device Combination Products

- Single-entity combination products (the components are physically, chemically or otherwise combined) (21 CFR 3.2(e)(1))
- Co-packaged combination products (the components are packaged together) (21 CFR 3.2(e)(2))
- Cross-labeled combination products (components are separately provided but specifically labeled for use together) (21 CFR 3.2(e)(3) or (e)(4))

Drug-Device Combination Products (DDCPs)

- Product-specific guidances (PSGs) for all drug-device combination products should include device-related language including
  - Drug with Complex Device
  - Drug with Non-Complex Device Combination

Drug with Complex Device DDCPs

In a complex DDCP with complex device, the drug constituent part is contained within or co-packaged with a product-specific device constituent part (either as a single entity or co-packaged) or cross-labeled for use with a specific device in which

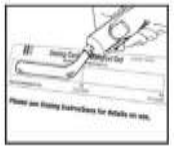
- The device design may impact drug delivery to the site of action and/or absorption (e.g., device design meters the dose,) and/or
- The user interface may have specific use considerations (e.g., when the product label indicates that users should be trained by a healthcare provider, when the device tracks the dose with an electronic system).

Drug with Complex-Device Examples

- Pre-filled syringes having a higher level of complexity (e.g., dual chamber syringe, multi-dose pen injector)
- Pre-filled auto-injector products for injectable formulations
- Orally inhaled and nasal drug products (such as metered-dose inhalers, dry powder inhalers, and metered nasal spray products)
- Inhalation products which require use with a specific delivery system
- Iontophoretic transdermal products
- Transdermal and topical delivery systems (TDS: historically, called “patches”)
- Metered-dose pumps for topical and transdermal formulations
- Implants with non-biodegradable device parts
- Intrauterine systems
- Electronic device systems (tracking dosage) including both software and hardware
- Vaginal systems

Drug with Non-Complex Device DDCPs

A device constituent part in a non-complex DDCP has a device design that may not impact drug delivery to site of action and/or absorption. Examples include


- Dosing cups for oral liquid formulation
- Dosing cards for topical ointments
- Simple pre-filled syringe and needle for injectable solutions where the device portion of the product does not play a key role in the dose delivery (e.g., the delivery is controlled by the user who administers the injection)
- Intravenous (IV) bags
- Eye droppers


https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/022122s010lbl.pdf
https://www.fda.gov/drugs/medication-errors-related-cder-regulated-drug-products/over-counter-otc-dosage-delivery-devices
https://www.fda.gov/drugs/buying-using-medicine-safely/what-you-should-know-about-eye-drops
Stock images for syringe and IV bag from Microsoft PowerPoint

Device and User Interface Language in PSGs for DDCPs

Important Dates: FDA Generic Drug Regulation & DDCPs

1984

Hatch-Waxman Amendments – 505(j) pathway for ANDAs established for generic drugs

1999

First draft Nasal guidance in 1999 includes device-related advice for nasal products. Guidance revised in 2003.

2012

GDUFA program established, and OGD becomes a CDER Super Office.

First inhaler PSG includes device-related language.

2019

OGD's Office of Research and Standards established a matrixed Device Evaluation Team to support pre-ANDA comparative user interface review for DDCPs

2021

Device Evaluation Team initiates the PSG Device language project to add device-related language to PSGs for all DDCPs

2021-2024

Device Evaluation Team increasingly integrated into ORS PSG development and revision processes; collaborative review process established.

DDCP = drug-device combination product

PSG Device and User Interface Language Processes

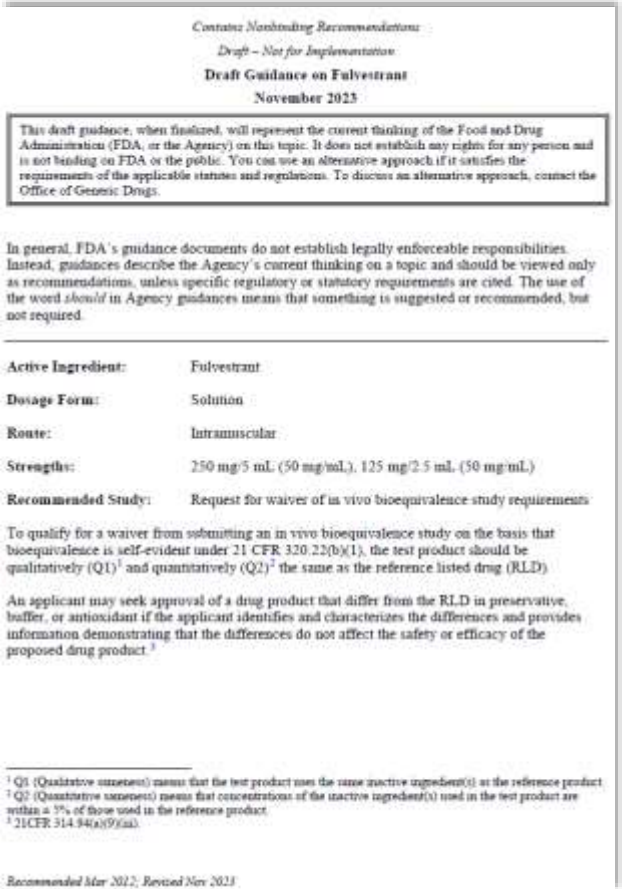
The device evaluation team (Team D) in Division of Therapeutic Performance I (DTP-I) in ORS/OGD reviews and adds or revises device and user interface language for the following PSGs.

- New DDCP PSGs
- Draft or final DDCP PSGs with no device and/or user interface language
- Draft or final DDCP PSGs with device and/or user interface language that require revision

Developing Device-Related Language

- Does the PSG being developed need device-related language – is the Reference Listed Drug (RLD, a listed drug identified by FDA as the drug product upon which an applicant relies in seeking approval of its ANDA) a drug-device combination product?
- If so, what are the device constituent parts?
- If unclear to the ORS Device Evaluation Team, send inquiry to the CDER Product Jurisdiction Officers

Device and User Interface Language



Contains Nonbinding Recommendations

Draft – Not for Implementation

Draft Guidance on Fulvestrant

November 2023

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the Office of Generic Drugs.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

Active Ingredient:	Fulvestrant
Dosage Form:	Solution
Route:	Intramuscular
Strengths:	250 mg/5 mL (50 mg/mL), 125 mg/2.5 mL (50 mg/mL)
Recommended Study:	Request for waiver of in vivo bioequivalence study requirements

To qualify for a waiver from submitting an in vivo bioequivalence study on the basis that bioequivalence is self-evident under 21 CFR 320.22(b)(1), the test product should be qualitatively (Q1)[1] and quantitatively (Q2)[2] the same as the reference listed drug (RLD).

An applicant may seek approval of a drug product that differ from the RLD in preservative, buffer, or antioxidant if the applicant identifies and characterizes the differences and provides information demonstrating that the differences do not affect the safety or efficacy of the proposed drug product.[3]

[1] Q1 (Qualitative sameness) means that the test product uses the same inactive ingredient(s) as the reference product.
[2] Q2 (Quantitative sameness) means that concentrations of the inactive ingredient(s) used in the test product are within ± 5% of those used in the reference product.
[3] 21CFR 314.94(a)(9)(iii).

Recommended Mar 2012; Revised Nov 2023

Section

Additional information:

Device:

The RLD is presented as a kit that consists of two prefilled syringes and two injection needles with needle guard. The prefilled syringe and injection needle with needle guard are the device constituent parts.

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

- Single-use, fixed-dose, prefilled syringe format
- Needle gauge and length
- Needle guard system

User interface assessment:

An abbreviated new drug application 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]

Document History: Recommended March 2012; Revised November 2023

Unique Agency Identifier: PSG_021344

The device and user interface recommendations are provided towards the end of the PSG document under the "additional information" section.

Device and User Interface Language

Statement about how RLD presented and identify device constituent parts

Aspects of RLD device constituent part to examine when designing/ choosing test device

User interface assessment – consistent language in all PSGs.

Additional information:

Device:
The RLD is presented as a kit that consists of two prefilled syringes and two injection needles with needle guard. The prefilled syringe and injection needle with needle guard are the device constituent parts.

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

- Single-use, fixed-dose, prefilled syringe format
- Needle gauge and length
- Needle guard system

User interface assessment:
An abbreviated new drug application 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]

Developing Device-Related Language

- How is the RLD presented?
- What are the RLD device constituent parts?

Device:
The RLD is presented as a kit that consists of two prefilled syringes and two injection needles with needle guard. The prefilled syringe and injection needle with needle guard are the device constituent parts.

PSG - Device Section

- What general device constituent features that affect user interface should be examined between the generic and the RLD?
  - Size
  - Shape
  - External Critical Design Attributes
  - External Operating Principles

FDA recommends that prospective applicants examine the size and shape, the external critical design attributes. and the external operating principles of the RLD device when designing the test device

PSG - Device Section

- Product-specific, unique, device constituent features that affect the product user interface

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

- Single-use, fixed-dose, prefilled syringe format
- Needle gauge and length
- Needle guard system

Single Product Presentations with General Device Features Language

- Ophthalmic Product

  The reference listed drug (RLD) product is presented in a single-dose vial with a dropper tip. The vial with dropper tip is the device constituent.

  FDA recommends that prospective applicants examine **the size and shape, external critical design attributes, and external operating principles** of the RLD device when designing the test device.

- Vaginal Product

  The reference listed drug (RLD) is presented in an assembly-required single-dose, prefilled, disposable vaginal applicator that is the device constituent.

  FDA recommends that prospective applicants examine **the size and shape, external critical design attributes, and external operating principles** of the RLD device when designing the test device.

Single Product Presentations with Device Language

- Transdermal Product

  The RLD is a transdermal delivery system and a drug-device combination product.

  FDA recommends that prospective applicants examine **the external critical design attributes, and the external operating principles** of the RLD device when designing the test device.

- Oral Product

  The reference listed drug (RLD) is presented in a bottle co-packaged with a bottle adapter and two oral syringes. The oral syringes are the device constituent parts.

  FDA recommends that prospective applicants examine the **size, shape and volume markings** of the RLD device when designing the test device.

Single Product Presentation – with Unique Device Features

- Periodontal Product

  The reference listed drug (RLD) product is presented as two prefilled syringes, which couple to form a mixing system, and a co-packaged blunt cannula. The two syringes and the cannula 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 device when designing the test device including the following characteristics:

  - The external diameter of the cannula
  - The length and flexibility of the cannula

- Rectal Product

  The Reference Listed Drug (RLD) is presented in a single-dose bottle with an attached, lubricated applicator tip. The bottle with applicator tip is a device constituent.

  FDA recommends that prospective applicants examine the size and shape, the external critical design attributes, and the external operating principles of the RLD device when designing the test (T) device including:

  - A lubricated rectal applicator tip

Single Product Presentation – with Unique Device Features

- Nasal Product

  The Reference Listed Drug (RLD) is presented as a gel in a metered nasal pump dispenser. The nasal pump dispenser is the device constituent part.

  FDA recommends that prospective applicants examine the size and shape, the external critical design attributes, and the external operating principles of the RLD device when designing the Test (T) device including:

  - Metered and multi-dose nasal pump design
  - Actuator (includes nasal tip) shape and size
  - Priming and cleaning processes

- Implant

  The Reference Listed Drug (RLD) is a sterile implant preloaded in a single dose, ready-to-use syringe with attached needle guard system. The implant and the syringe with attached needle guard system are device constituents.

  FDA recommends that prospective applicants examine the size and shape, external critical design attributes, and the external operating principles of the RLD device when designing the Test (T) device including:

  - Implant size and shape
  - Sterile, single-dose, fixed-dose, prefilled syringe format
  - Needle features: siliconized, triple-beveled, gauge, and length
  - Needle guard system

Multiple Product Presentations

Device:
The RLD has three different presentations: (1) an auto-injector, (2) a pre-filled syringe, or (3) a kit that consists of a vial of drug co-packaged with a syringe with staked needle. The auto-injector, pre-filled syringe, and co-packaged syringe with needle are the device constituent parts for these presentations respectively.

FDA recommends that prospective applicants examine the size and shape, the external critical design attributes, and the external operating principles of the RLD device when designing the Test device including:

1. Auto-injector presentation:
    a. Single-dose, fixed-dose, auto-injector format capable of delivering the same dose as the RLD product
    b. Medication viewing window
    c. Needle gauge and length
2. Pre-filled syringe presentation:
    a. Single-dose, fixed-dose, prefilled syringe format with staked needle
    b. Needle gauge and length
3. Kit:
    a. Syringe with staked needle
    b. Needle gauge and length

Resources

- FDA Guidance Document Search: Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA: Draft Guidance for Industry
- CDER Manual of Policies & Procedures | MAPP: MAPP 5240.10: Classifying Approved New Drug Products and Drug-device Combination Products as Complex Products for Generic Drug Development Purposes
- 21 CFR 3.2
- Product-Specific Guidances for Generic Drug Development
- https://www.fda.gov/combination-products/about-combination-products/combination-product-definition-combination-product-types
- https://www.fda.gov/combination-products/about-combination-products/frequently-asked-questions-about-combination-products
- DDCP 101 – Identifying, Developing, and Evaluating Generic Drug Device Combination Products (DDCP)
- Drug-Device Combination Products: Updates and Challenges with Demonstrating Generic Substitutability

Summary

- All PSGs for CDER led drug-device combination products should include device related language.
  - ORS is working to add device related language to older PSGs for DDCPs.
- The device section identifies the device constituent parts of the combination product.
- The user interface section directs the user to the guidance with detailed information to conduct a user interface assessment for a proposed generic referencing a DDCP RLD.

Questions?

Karthika Natarajan
Staff Fellow,
DTP-1 | ORS | OGD
CDER | U.S. FDA

[Karthika.Natarajan@fda.hhs.gov]

Closing Thought

Engage with FDA early and often to request feedback on the proposed generic drug-device combination product device constituent part and user interface through controlled correspondences or product development meetings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