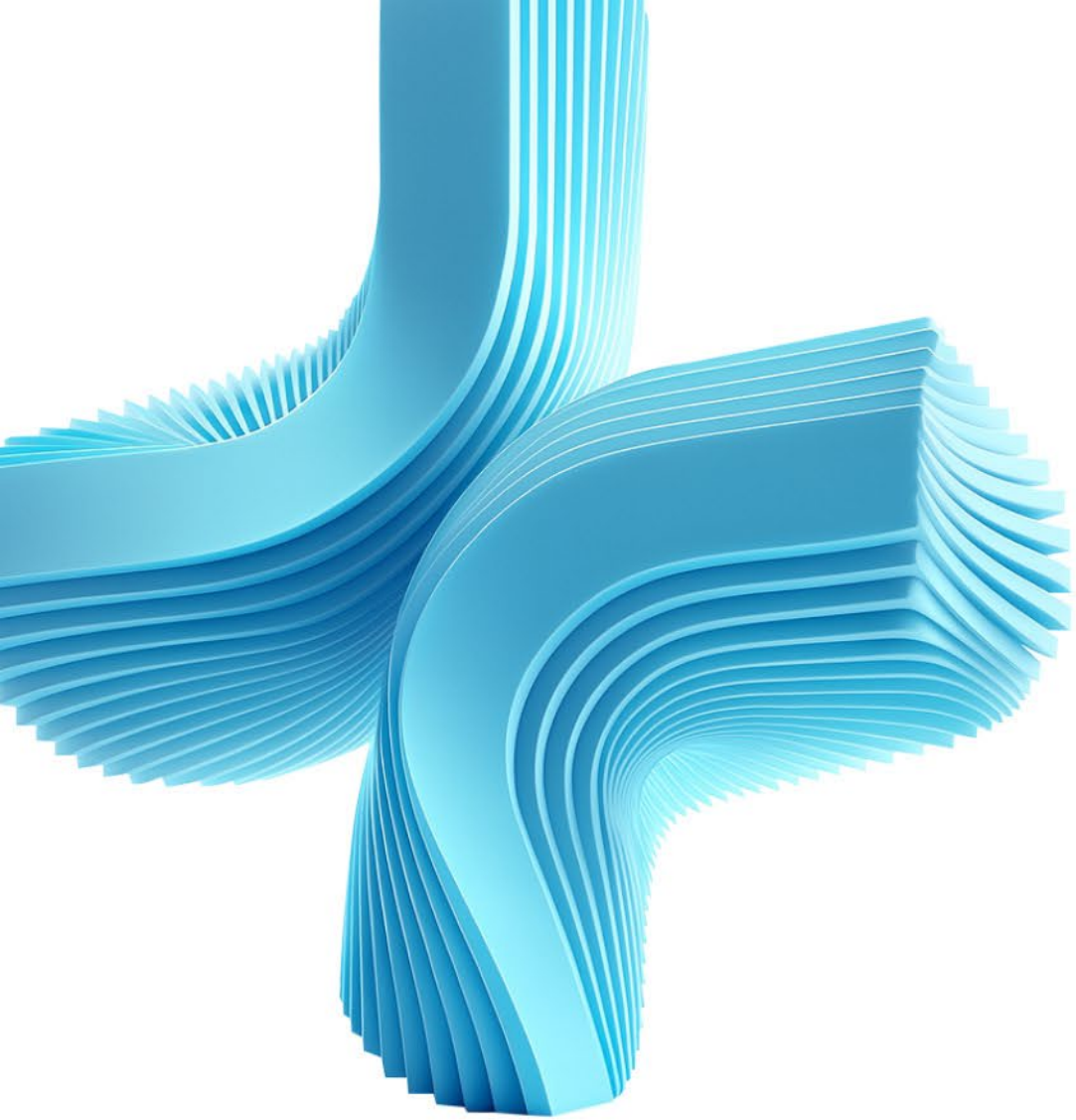


Device Considerations for Therapeutic Equivalence and Interchangeability

NOVEMBER 2-4, 2026
#GRXBIOSIMS | GRXBIOSIMS.ORG



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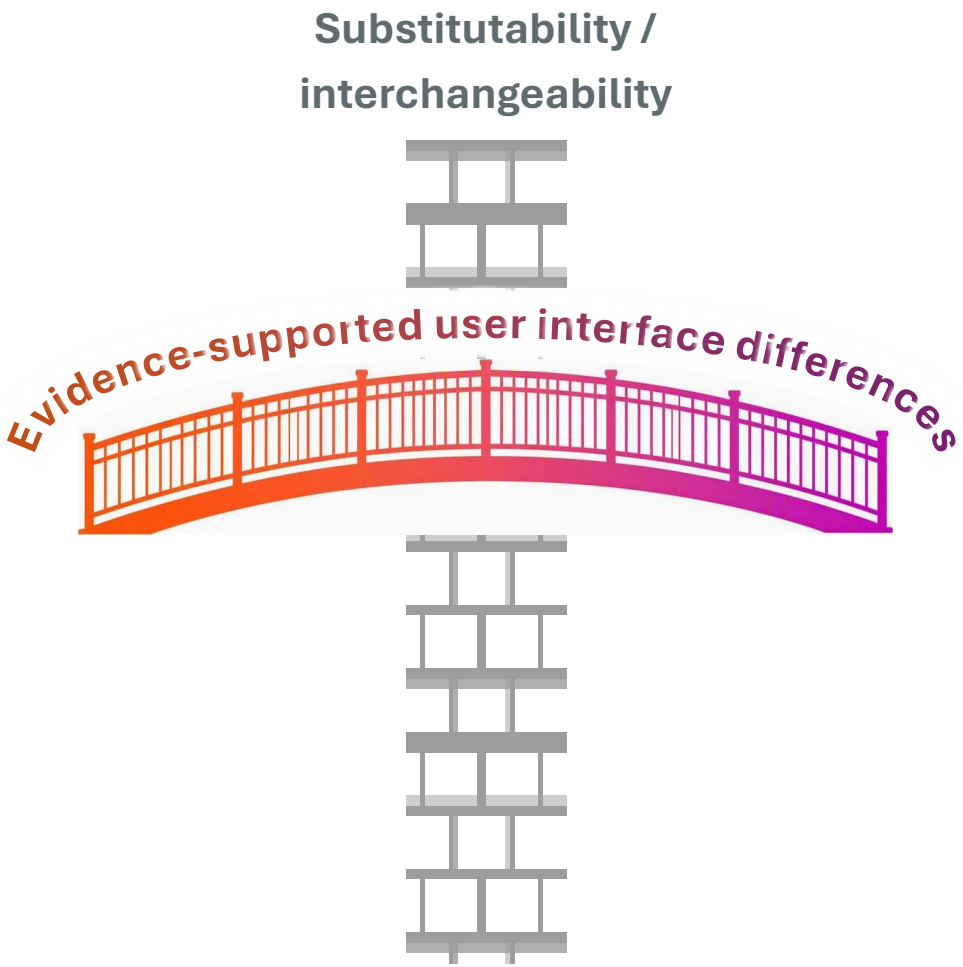
Generic/biosimilar combination product user interface: need for difference, case for flexibility

Need for difference

- Outdated RLD/RP user interface
- Known use errors with RLD/RP
- Competition among generics companies
- Exclusivity contracts for off-the-shelf device constituent parts
- Patents, trademark and intellectual property

Case for flexibility

- Use state-of-the art device constituent parts
- Solving safety and/or effectiveness concerns by addressing known use errors
- Implementation of user interface improvements

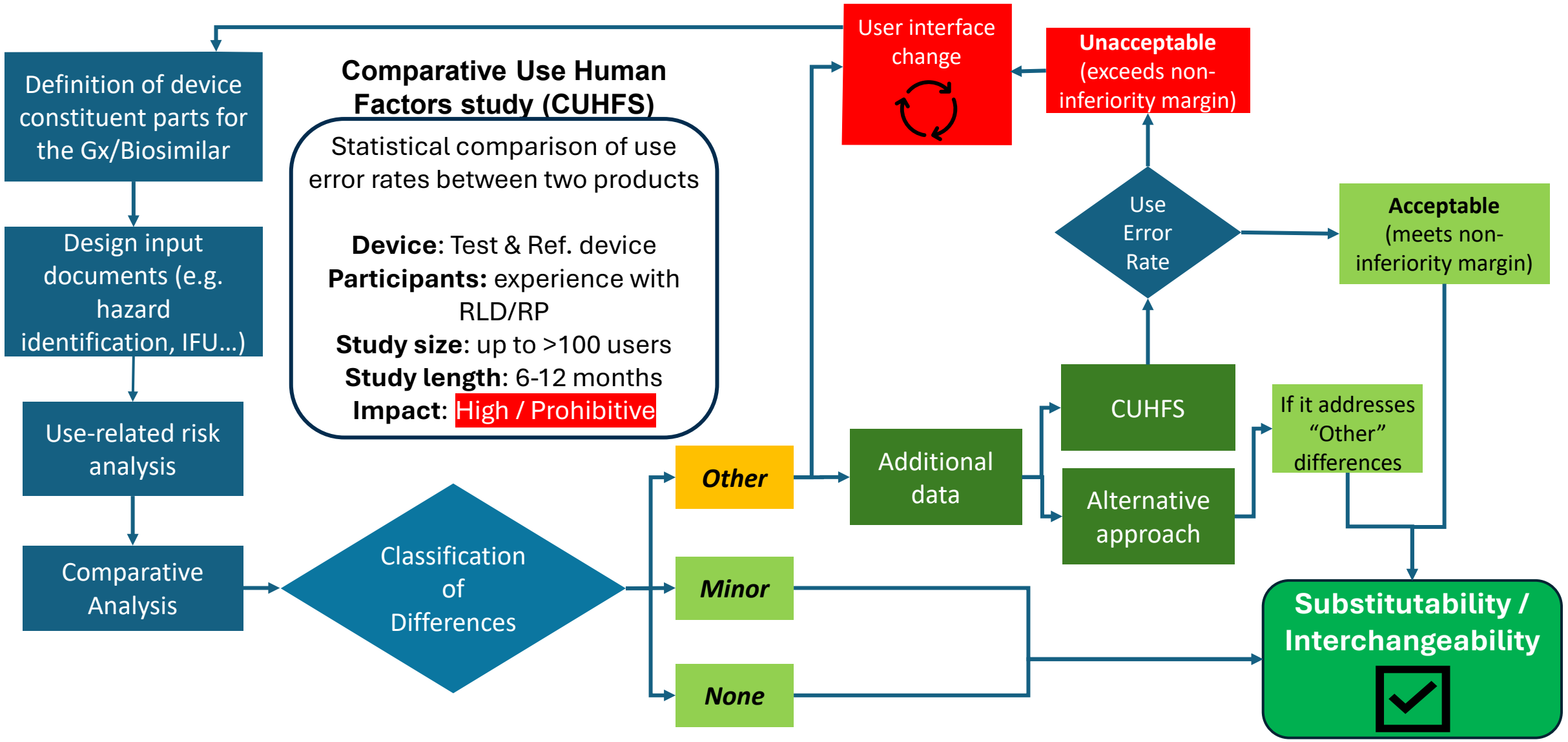


Generic/biosimilar combination product

- Leverage findings of safe and effective use from the RLD/RP
- Establish that the Generic/Biosimilar can be substituted for the reference product at pharmacies without physician intervention or additional training

RLD: reference listed drug; RP: reference product

How substitutability can be demonstrated: comparative analysis and CUHFS or “alternative approach”



HF assessment informs device development throughout

	Feasibility / Device selection	Design development		Submission
	Feasibility to submission: ~3-4 years			
Drug	Define target molecule and product profile	Development and tech transfer	Registration batches and stability data	**Drug / Device compatibility**
Device	Manufacturing needs, user needs and development plan	Design inputs/Design outputs and verification	Design transfer and complete verification and validation	
HF	**Preliminary HF assessment** • Assess users, use context • Compare critical external design attributes with the RLD/RP	**In-depth HF assessment** • Complete COAN • If other design differences are identified, CUHF study or additional data may be required	**Finalize HF activities** • Document outcome of HF activities during development	**HF evidence package** Provide the human factors information for submission

Unfavorable HF outcome at this stage can significantly delay the submission

Device selection and design freeze are critical "points of no return": later changes to the user interface (except labeling) could set the project back by years and jeopardize its commercial viability

Real-World Challenges and Opportunities

	CHALLENGE		POTENTIAL SOLUTION
Study design	Limited published RLD/RP HF data – required input for CUHF study setup missing	→	Allow qualitative evaluation instead of quantitative statistical analysis of human behavior
	Most stringent error margin must be applied across all critical tasks	→	Apply task-specific error margins based on severity of harm
	One-time use does not reflect chronic treatment	→	Permit inclusion of learning effects in the assessment
Recruitment	New user populations, second-line treatment, other generics and pilot studies limit participant pool for later CUHF studies	→	Permit e.g. surrogate users experienced with the same device in another indication, or naïve users trained on the RLD/RP
	Restrictive criteria exclude assistance or guardian presence	→	Allow assistance and guardian presence if representative of real-world use
Costs and timeline	Need for formative/pilot studies, RLD/RP sample cost and availability; need for third-party recruiters and studies in multiple cities	→	Test only the proposed device, comparing RLD/RP-experienced and naïve users. Permit surrogate-users (see above)

U.S. Food & Drug Administration

AAM GRx/Biosims Meeting | November 2026 | North Bethesda Conference Center

GDUFA Research Program for Generic Drug-Device Combination Products (DDCPs)

Markham C. Luke, MD PhD
Division of Therapeutic Performance I | Office of Research and Standards
Office of Generic Drugs, CDER, U.S. FDA

Major GDUFA-funded DDCP Projects

The Questions

- Can we execute a noninferiority CUHF study as described in the 2017 FDA Draft Guidance on CA and possible approach for statistical CUHF for DDCPs in ANDAs?
- Can we do this study for a pen or autoinjector product to show interchangeability or device substitutability without compromising patient use in a significant manner? Select a reference drug that is used at home and potentially with patents that present challenges for generics.

The Projects

IDIQ Task Order #1 – Completed and Published

Randomized, crossover, simulated-use study with NI testing – 10% prespecified margin, Tango score interval data pairs

Study data, sample size selection, etc. available to address important knowledge gap

Demonstrates substitution of manual ”dose-selector barrel extension” pen for partially automated multiuse pen

IDIQ T.O. #2 – Completed/Publishing Pending

Evaluation of substitutability of a different fully automated pen injector

Major GDUFA-funded DDCP Projects

The Questions

- Can we use real-world evidence to evaluate post-approval generic drug adoption and clinical outcomes for generic drugs with acceptable device constituent differences?
- Can we develop and standardize methods to compare generic vs. reference products using RWE (i.e. propensity modeling and analysis of clinical outcomes parameters)?

The Projects

RWE Collaborative Grant (BWH and UCLA)

Multiple ANDA products evaluated – OINDP DPI, injectable, transdermal patch

Demonstrated no significant difference between reference and test approved ANDA drugs for multiple prespecified clinical outcomes measures using large outcomes data

Developed methods to conduct propensity analysis for generic drug substitution evaluations

Multiple FDA Intramural DDCP Projects

- Understanding the supply chain for pen and autoinjector devices (this included devices used for biosimilars as there is overlap in the design and supply of these devices).

- Laboratory evaluation of the performance of various drug products in response to post-approval reports of device use difficulties (multiple investigations in conjunction with White Oak and St. Louis laboratories).

- Laboratory evaluation of design and performance of various drug-device combination products, including with sensor/electrical components (in conjunction with FDA St. Louis laboratory).

- Evaluation of excipient compositions of transdermal patches to enable Q1Q2 considerations for these products with the intent of reducing the need for clinical sensitization comparison studies.

GRx-Biosims

Kimberly Witzmann, MD

Deputy Director

Office of Safety and Clinical Evaluation

OGD/CDER

Food & Drug Administration (FDA)

Comparative Analyses Framework

Consider any identified differences in the context of the overall risk profile of the product

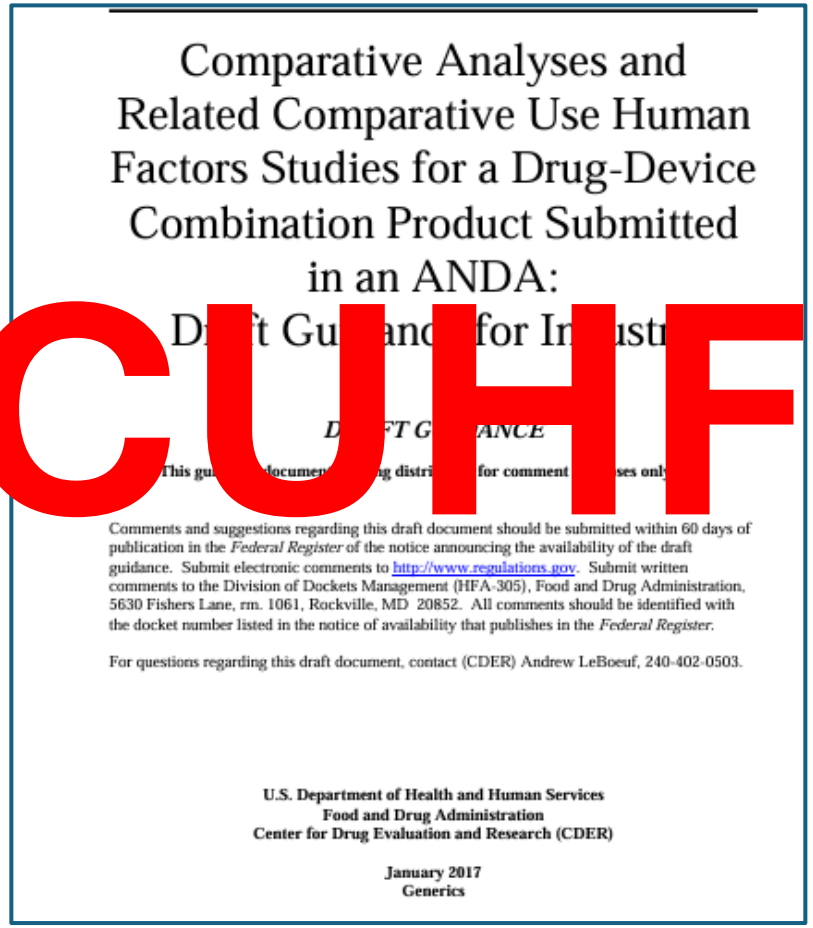
- *No Differences*
- ***Minor** Design Difference*
  - *If a difference in the user interface of the proposed generic combination product in comparison to the user interface of the RLD does not affect an external critical design attribute impacting a critical task*
- ***Other** Design Difference*
  - *If any aspect of the comparative analyses suggests that a 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*

Comparative Analyses- Other

"In such cases, the potential applicant should first strongly consider modifying the design of the user interface (e.g., delivery device constituent part) to minimize differences from the RLD.

Alternatively, if such differences are present in the fin[illegible]sig[illegible]e[illegible]ser in[illegible]erf[illegible]d th[illegible]posed g[illegible]neric [illegible]om[illegible]nati[illegible]n pro[illegible]uc[illegible] **FDA m[illegible]y r[illegible]quest t[illegible]at ap[illegible]ica[illegible]ts pr[illegible]vide[illegible] dd[illegible]ional [illegible]f[illegible]rmation a[illegible]/or [illegible]ata,** [illegible]uch[illegible]s da[illegible] fr[illegible]m a co[illegible]par[illegible]ive us[illegible] human factors study, **to address whether the differences identified in the user interface introduce a risk that might impact the clinical effect or safety profile of the generic** combination product as compared to the RLD when the generic combination product is substituted for the RLD."

OTHER ≠ CUHF



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

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This gu[illegible] document[illegible]g distri[illegible] for comment [illegible]ses 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*.

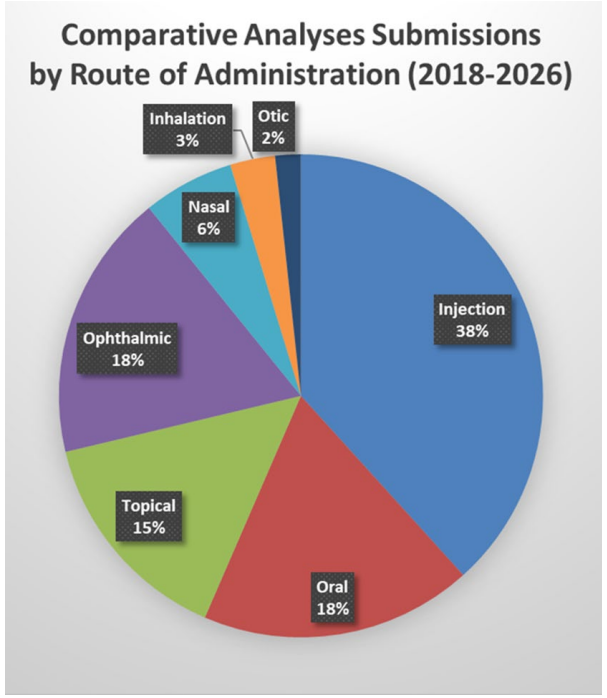
For questions regarding this draft document, contact (CDER) Andrew LeBoeuf, 240-402-0503.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

January 2017
Generics

ANDA User Interface Experience 2018-2026

- Almost 1,500 ANDA submissions of drug-device combination products for which Comparative Analyses were assessed
- Between 15-20% of the 1,500 combo ANDAs had **other** design differences
  - Some required justification only
  - Others had additional data within their development program that answered the interface question
  - Still others have used data from an outside source, like literature
- Approximately 1.5% of submissions provided CUHF studies as their "additional information and/or data" when found to have an other design difference



Ensure your additional info/data demonstrates that your design difference does not impact the clinical effect and safety profile when used in accordance with labeling!

Come talk to us!!

U.S. FOOD & DRUG ADMINISTRATION

Center for Drug Evaluation and Research

fda.gov/biosimilars

DEVICE USER INTERFACE CONSIDERATIONS - BIOSIMILAR AND INTERCHANGEABLE PRODUCTS

GRx + Biosims

November 2, 2026

Cristina Ausin, Ph.D., Master Biologist
Office of Therapeutic Biologics and Biosimilars (OTBB)
Office of New Drugs/Center for Drug Evaluation and Research
US Food and Drug Administration

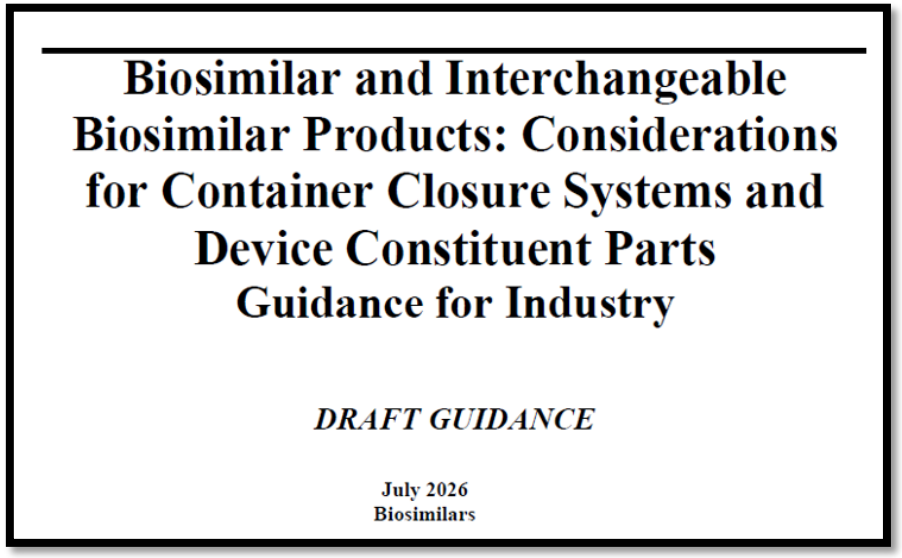
Current User Interface-Related Expectations for 351(k) Applications

URRA + Comparative Analyses → Classification of Differences

- None
- Minor

→ **No additional Data are Needed**

- Other → **Additional Data/Information are Needed**
  - → Biosimilar → HF Validation
  - → Interchangeable →
    - CUHF Study or
    - Appropriately Designed HF Study* or
    - Other Scientific Information



Biosimilar and Interchangeable Biosimilar Products: Considerations for Container Closure Systems and Device Constituent Parts
Guidance for Industry

DRAFT GUIDANCE

July 2026
Biosimilars

*It may be feasible to develop a single human factors study that is appropriately designed to support licensure of the proposed combination product as both biosimilar and interchangeable.

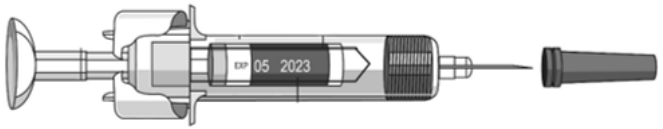
Current User Interface-Related Expectations for 351(k) Applications

- To be licensed under Section 351(k) of the PHS Act, any design difference cannot result in the following:
  - A clinically meaningful difference from the RP in terms of S&E
  - A different route of administration, dosage form, and strength as the RP
  - A conditions of use (e.g., indication, dosing regimen) not previously approved for the RP
  - Otherwise preclude licensure as a biosimilar or interchangeable biosimilar product
- For proposed presentations not marketed for the RP
  - It is likely that additional data/information will be needed to characterize the impact of differences in user interface and support approval

Presentations not Marketed for the RP: Case Study



Pyzchiva (ustekinumab-ttwe) AI



Stelara (ustekinumab) PFS

Summary Review available at drugs@FDA: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2025/761373Orig1Orig2s001,761425Orig1Orig2s001CrossR.pdf

Approval Date(s) and History, Letters, Labels, Reviews for BLA 761373

Original Approvals or Tentative Approvals

CSV | Excel | Print

Action Date	Submission	Action Type	Submission Classification	Review Priority; Orphan Status	Letters, Reviews, Labels, Patient Package Insert	Notes
04/30/2025	ORIG-2	Approval		N/A	Label (PDF) Letter (PDF)	
06/28/2024	ORIG-1	Approval		N/A	Label (PDF) Letter (PDF) Review	

Showing 1 to 2 of 2 entries

Supplements

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Action Date	Submission	Supplement Categories or Approval Type	Letters, Reviews, Labels, P… Package Insert	Note
06/27/2025	SUPPL-1	Supplement	Label (PDF) Letter (PDF) Summary Review (PDF)	

Presentations not Marketed for the RP: Case Study

1. The Applicant provided adequate product quality information including performance and compatibility data
2. The Applicant provided a justification for not conducting a PK study following principles in the Bridging Guidance (https://www.fda.gov/media/133676/download)
3. User interface assessment
    - Conducted Comparative Analyses (formerly called Threshold Analysis) of user interface of proposed AI vs. RP PFS (physical, tasks, labeling)
    - Identified "*other differences*"
    - Leveraged results from a HF validation study using the same AI for another product the Applicant had a right to reference
    - Conducted CUHF study comparing proposed AI to RP PFS

The Negative Transfer Assumption

Ariane O. Conrad, PharmD, BCACP, CDCES, FISMP

Associate Director for Human Factors

Division of Medication Error Prevention and Analysis I (DMEPA I)

Office of Medication Error Prevention & Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

What Is Negative Transfer and Why Does It Matter?

- Transfer of training or learning occurs with the use of everything, including medical devices*
  - **Positive transfer** → the lessons learned using one device apply correctly to another device
  - **Negative Transfer** → the lessons learned using one device do not apply to another one, leading to a use error

- Impact on Regulatory Expectations:
  - FDA expects that users of a generic or biosimilar interchangeable combination product can use the product when substituted for or switched from the reference listed drug (RLD) or reference product (RP) without intervention from a healthcare provider (HCP) or additional training
  - When a proposed product differs in design as compared to the RLD or RP, applicants need to account for the impact of those differences on the risk of use errors with their proposed user interface
  - Use errors attributable to negative transfer may trigger product development and data needs:
    - Other design differences → risk of use errors → additional information and/or data (such as data from a comparative use human factors study)

*American National Standards Institute and Association for the Advancement of Medical Instrumentation, 2025, ANSI/AAMI HE75:2025: Human Factors Engineering—Design of Medical Devices

Beyond Negative Transfer: Why FDA Requires Human Factors Data

- **A Common Misconception We See:** Human factors (HF) study data is only needed in instances where there is a risk of use errors due to negative transfer between the RLD/RP and the proposed product. If the product is "simple to use", data is not necessary.

- However, **from the Agency's perspective**, in the context of HF studies designed to support other design differences, negative transfer may be only one possible root cause for use errors.
  - Product design issues related to the other design differences may also be a root cause for use errors
  - Early identification of possible causes for use errors during formative testing can help determine appropriate risk controls during product development

Key Message

- If other design differences are identified during the comparative analyses process, negative transfer is only ONE possible root cause for errors that may be attributed to design differences within the context of a HF study
  - Additional data may be needed to support your product development and evaluate proposed risk controls if design differences are identified

- Consider if all use-related risks associated with your specific combination product have been adequately characterized and addressed (*versus* focusing only on those risks related to negative transfer)

- If you determine that HF study data is not needed for your intend-to-market user interface based on your comparative analyses and risk analysis, **consult FDA early** to reach alignment regarding your data needs


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