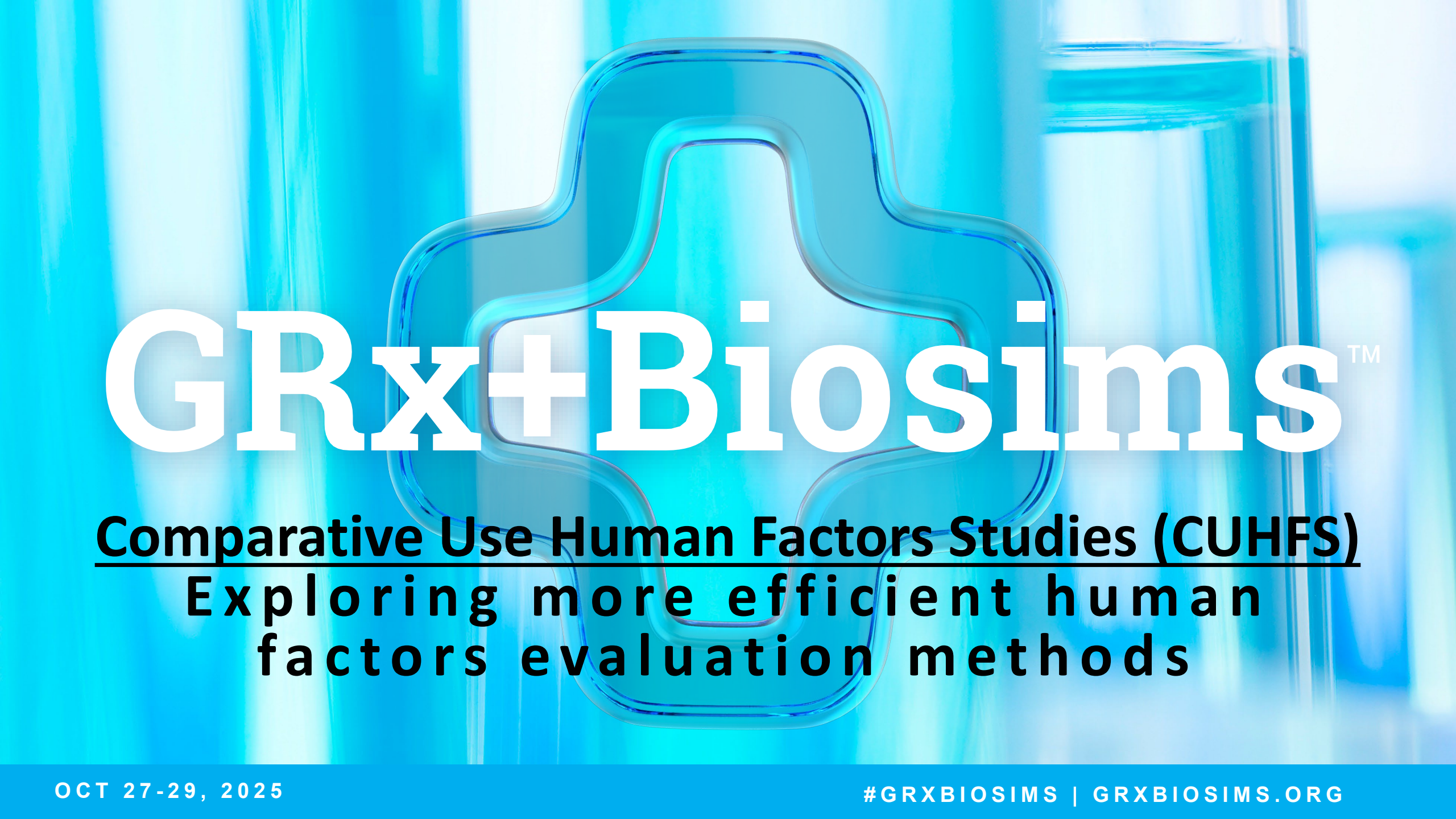


Comparative Use Human Factors Studies (CUHFS)

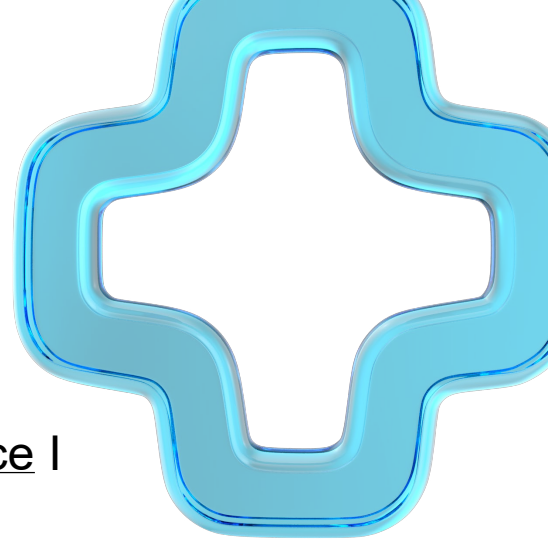
Exploring more efficient human factors evaluation methods

SESSION OBJECTIVE

This session will explore human factors evaluation framework for both generic and interchangeable combination products with the following key objectives:

- Understand the current framework and challenges associated with Comparative Use Human Factors studies (CUHFS)
- Discuss proposals for improvements and alternatives to CUHFS
- Continue the Industry & FDA conversation regarding implications and opportunities for future product submissions and guidance

Participants



FDA Participants

- **Andrew Clerman,** M.D. Ph.D. Acting Lead Physician, Division of Therapeutic Performance I (DTP I), ORS, OGD, CDER, FDA (Andrew.Clerman@fda.hhs.gov)
- **Andrew Fine**, PharmD, BCPS. Senior Advisor, Division of Clinical Review, Office of Safety and Clinical Evaluation OGD, CDER, FDA (Andrew.Fine@fda.hhs.gov)
- **Cristina Ausin**, Ph.D. Scientific Reviewer, Office of Therapeutic Biologics and Biosimilars (OTBB), Office of New Drugs (OND), CDER, FDA (Cristina.Ausin@fda.hhs.gov)

Industry Participants

- **Carrie O'Donel,** MS, Associate Director, MS&T, External Manufacturing, Teva (Carrie.ODonel@tevapharm.com)
- **Johannes Keuschnigg,** Ph.D. Portfolio Head Regulatory Devices Sandoz (Johannes.Keuschnigg@sandoz.com)
- **Chris Lamanna,** Ph.D. Head Regulatory Devices Sandoz (William.Lamanna@sandoz.com)

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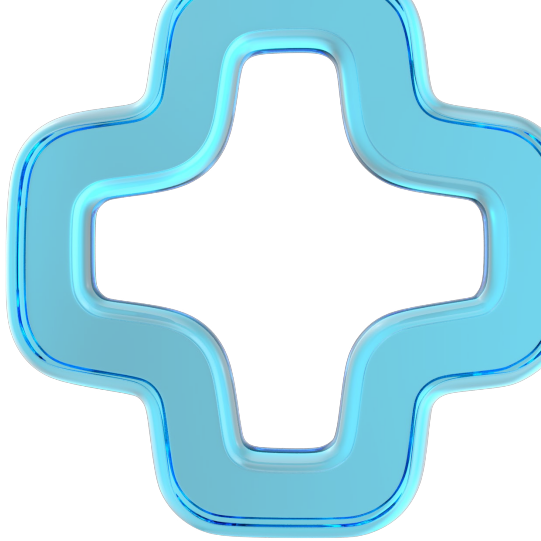
CUHFS background and challenges

Johannes Keuschnigg, Ph.D.

Portfolio Head Regulatory Devices

Sandoz

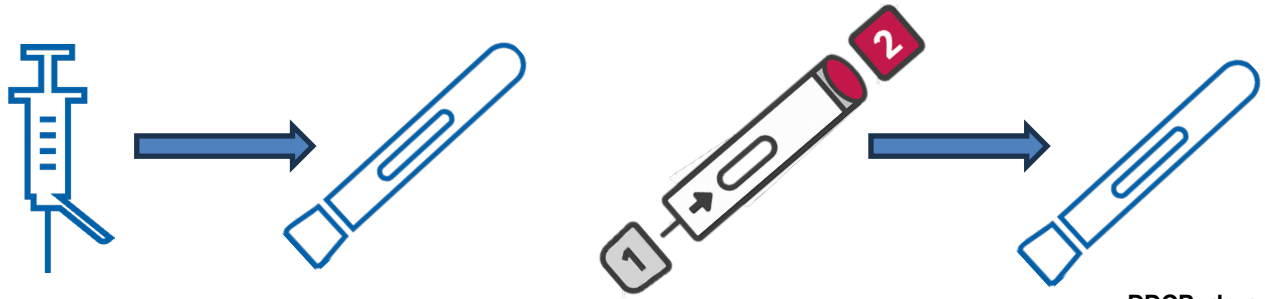
Substitutable/interchangeable DDCPs must be non-inferior to RP/RLD from a usability perspective when substituted at pharmacy level



Pre-requisite for DDCP development: ensuring that the product is safe and effective

Additional requirement for substitutability/interchangeability: ensure that intended users can safely use the DDCP in place of RP/RLD following pharmacy level substitution without HCP intervention or additional training

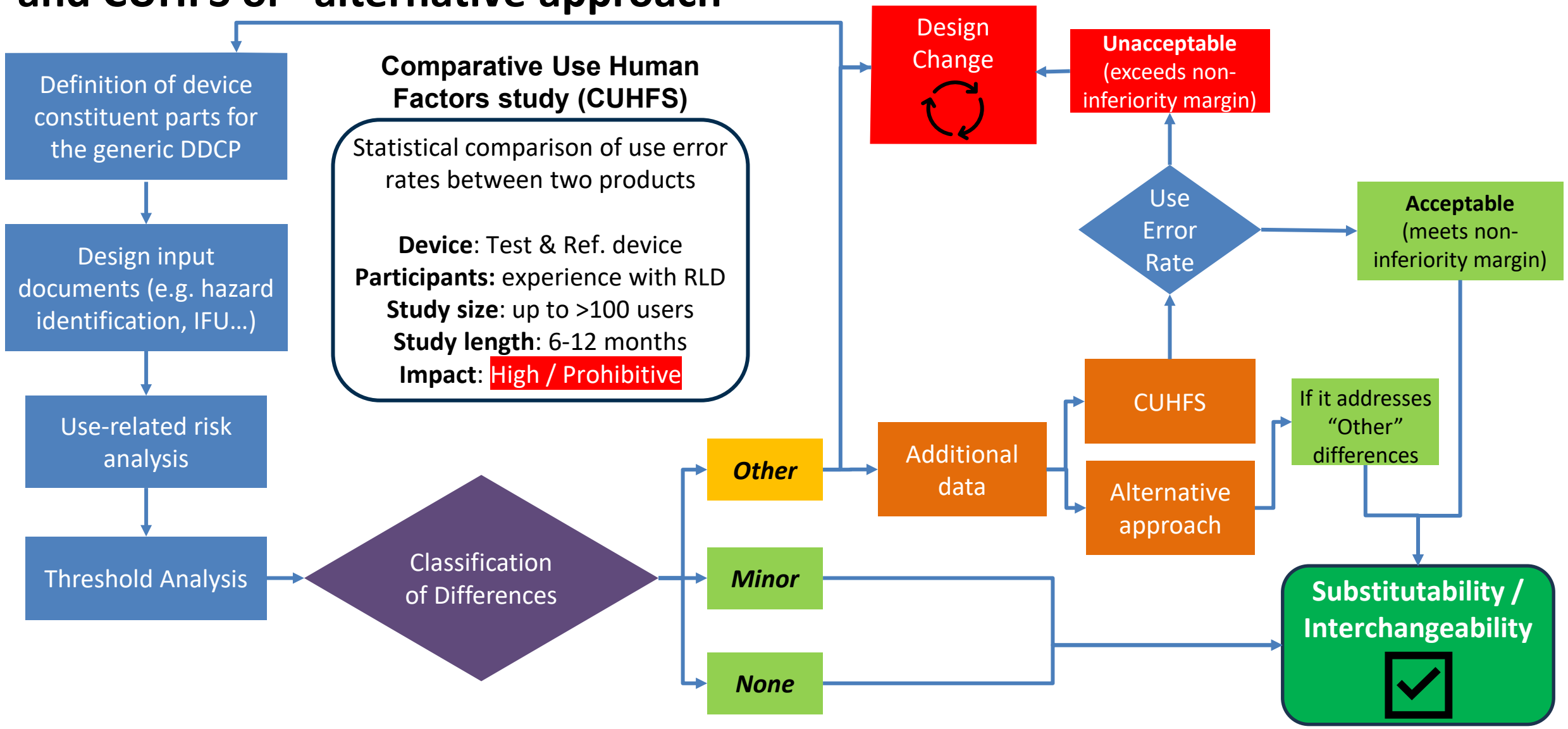
Concern: users have experience with RP/RLD and might be confused by differences in the substitutable/interchangeable product (negative knowledge transfer/mental models)



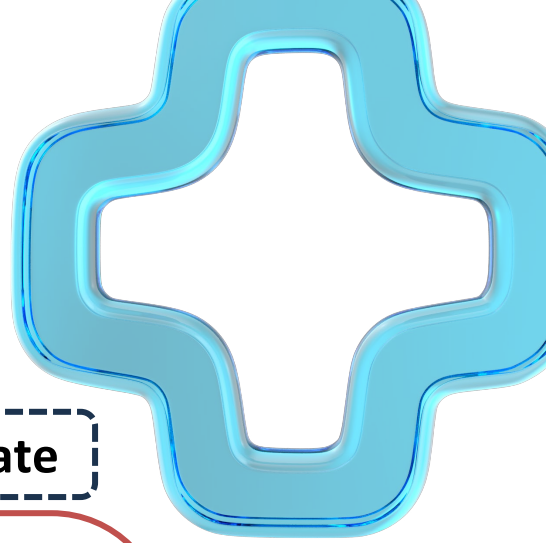
Note: the terms "Substitutability" and "RLD" are used throughout the presentation. They are intended to cover also the biosimilar terms "Interchangeability" and "RP"

DDCP: drug-device combination product; RLD: reference listed drug; RP: reference product; HCP: healthcare professional

How substitutability can be demonstrated: threshold analysis and CUHFS or "alternative approach"

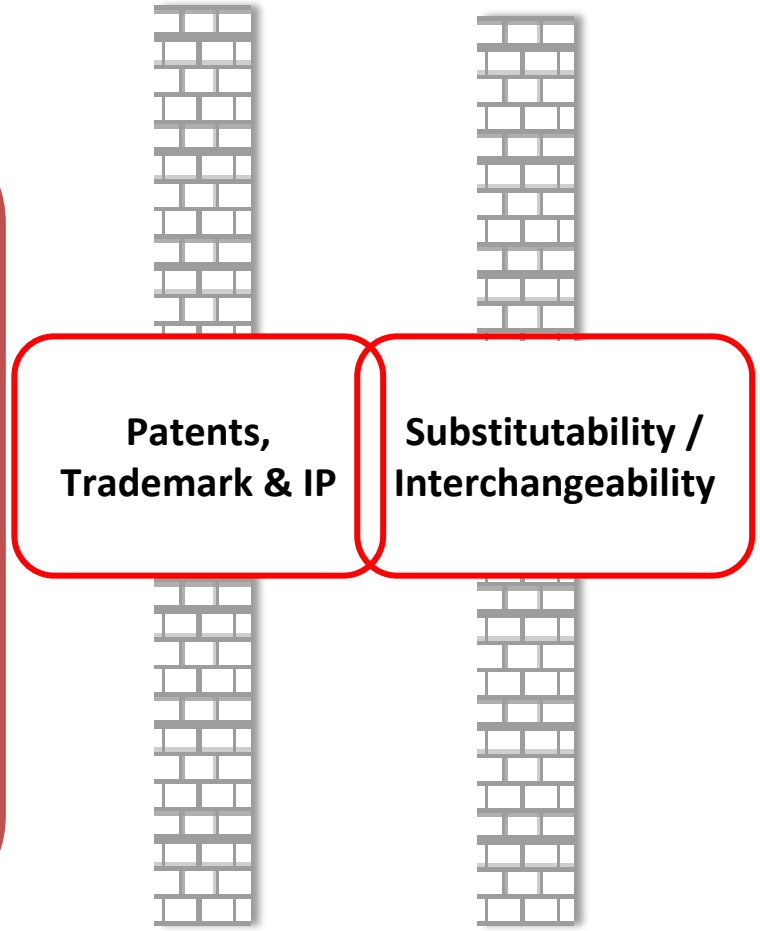


Generic DDCPs face specific challenges in matching the RLD user interface with an increasing need for patient-friendly innovation



Differentiation drivers

1. RLD with older device constituent parts
2. Known use errors with RLD
3. RLD device constituent parts unknown
4. Wish to improve user experience
5. Competition among generics companies
6. Wish to use platform technology/products



Objective / ideal state

1. Development of state-of-the art DDCPs
2. Solving safety and/or effectiveness concerns by addressing known use errors
3. Implementation of user interface improvements

Access Innovation Flexibility

BsUFA + GDUFA Research initiatives, real world experience and collaborative exchange can improve clarity & guidance

Challenge

CUHFS statistical model:
Non-inferiority model applies most stringent error rate margin "d" across all critical use tasks

CUHFS study design:
Challenges in recruiting, originator availability and cost

Opportunity

Refine CUHFS model to improve assessment of actual patient risk

- Application of error margin "d" to individual critical tasks based on severity of harm
- Account for learning effect (likelihood of repeated error) for individual critical tasks

Alternative validation approaches

- Validation study with substitutable device only
  - Compare substitutable device usability between RLD users vs. naive users

CUHFS waiver based on data & experience

- Leverage platform CUHFS data, predictive studies or real-world evidence when justified

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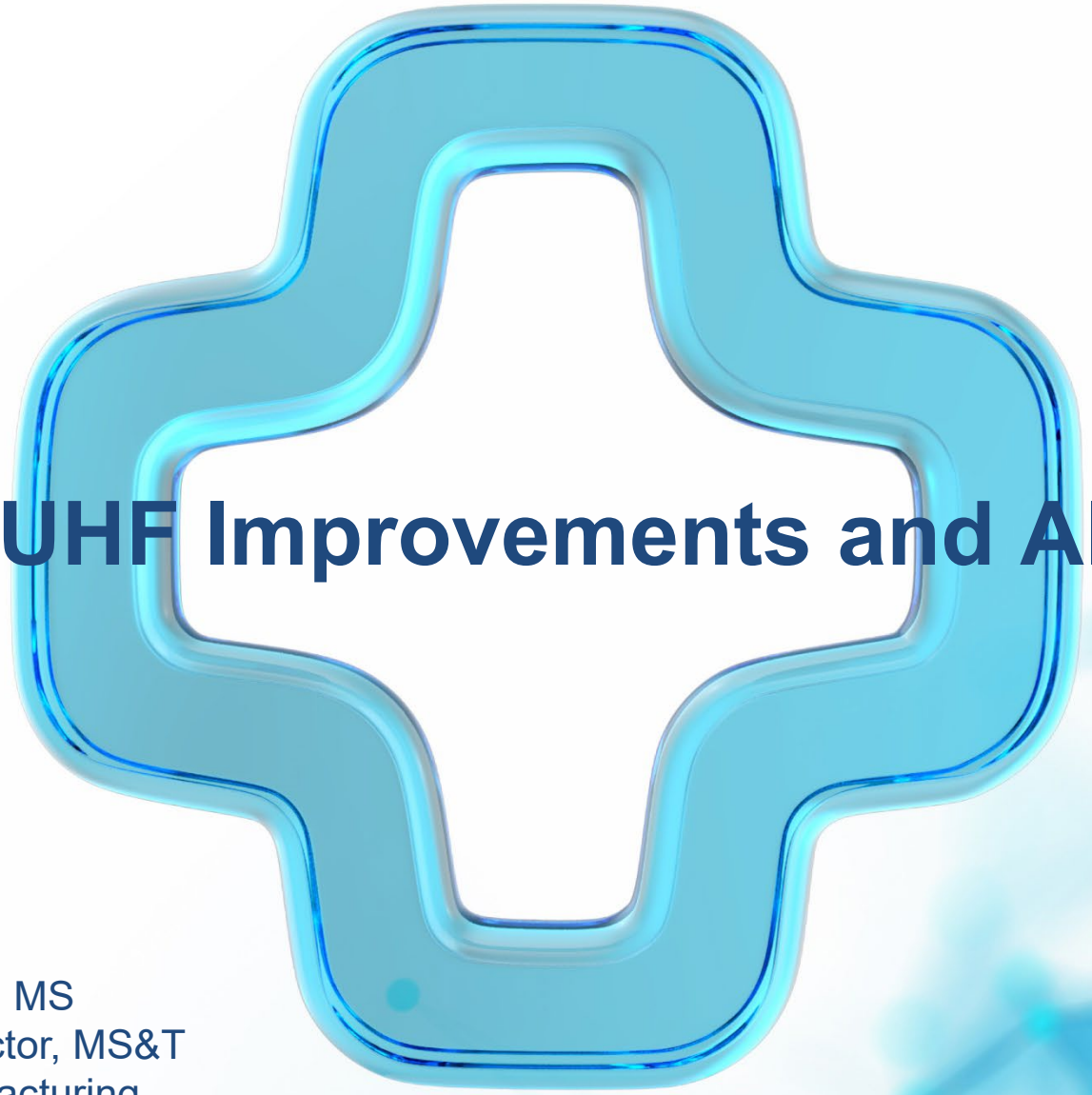
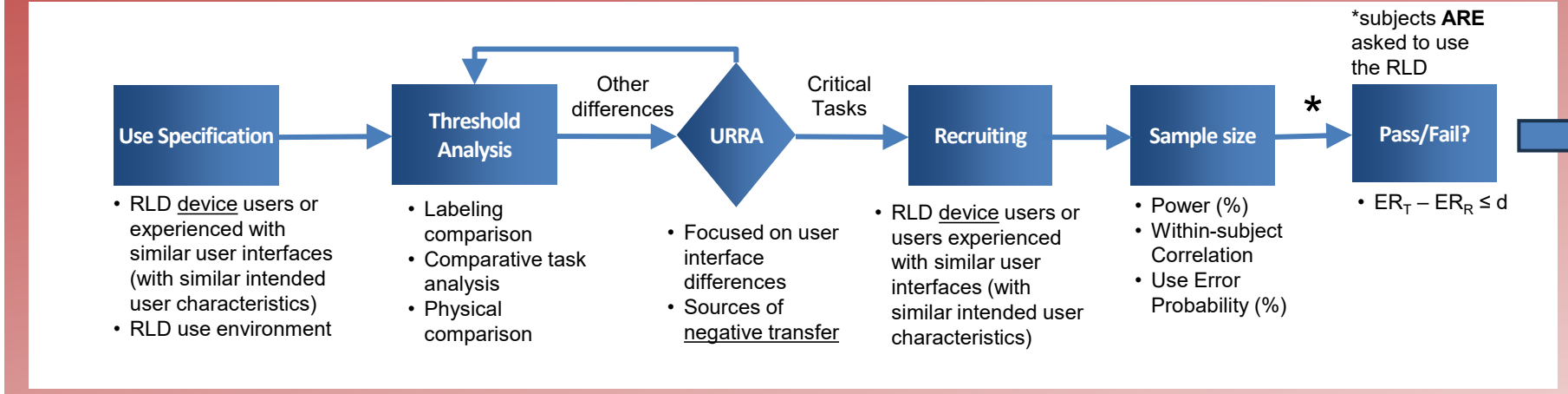


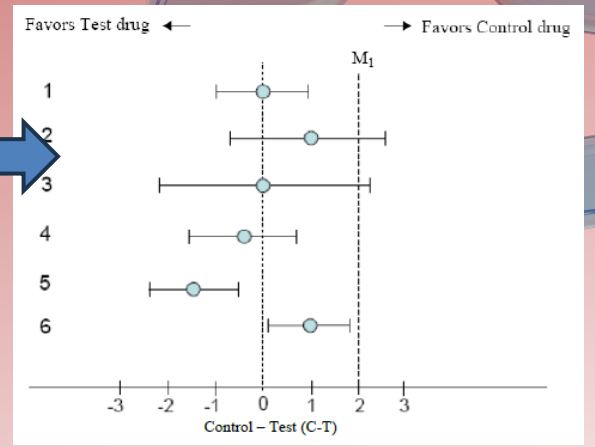
CUHF Improvements and Alternatives

Carrie O'Donel, MS
Associate Director, MS&T
External Manufacturing
TEVA

Based on the results from the study published in October 2025 issue of OndrugDelivery:
O'Donel C, Akouka H, DeStefano M, Sanchez-Torres L, "Alternative Approach for Device Substitutability: Human Factors Studies for Generic and Biosimilar Products". ONdrugDelivery, ***Issue 178 (Oct 2025)****, pp 28–33.*

Comparative Use Human Factors (CUHF)/Clinical Non-inferiority





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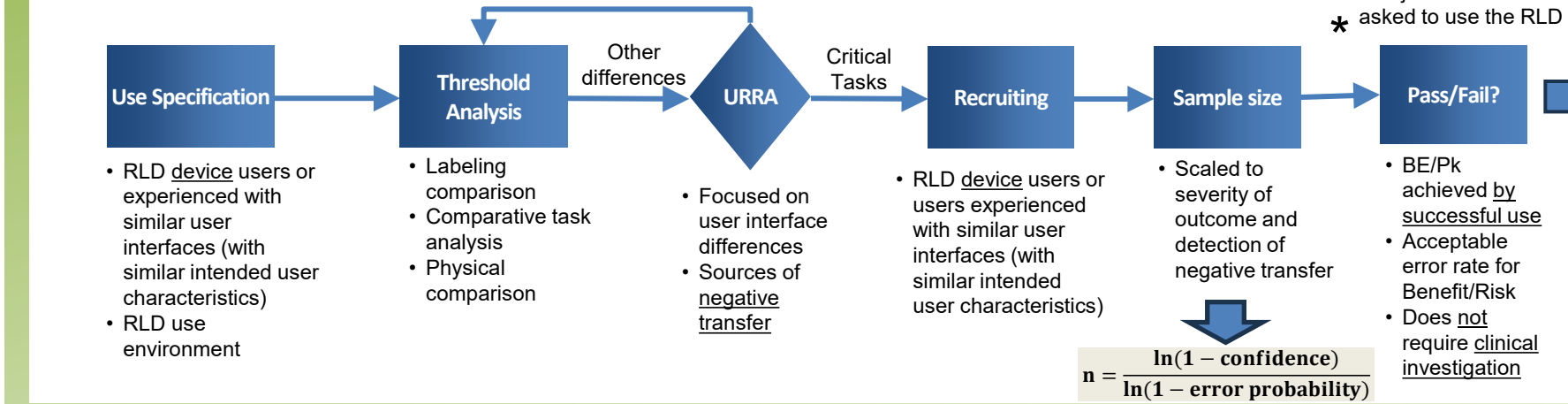
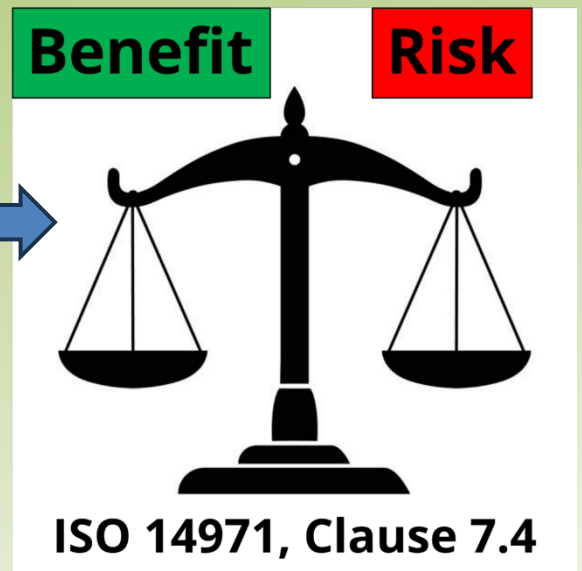
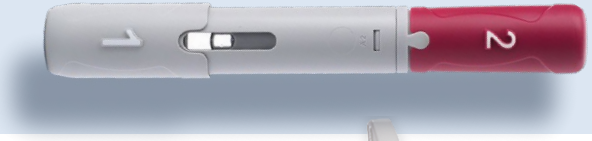
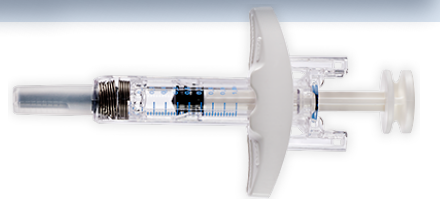
IEC 62366 Human Factors Validation adjusted for "Substitutability"





Targeted Devices and Indications

GOAL: Explore device crossover and will seek to challenge **the mental models** of experienced 4-step and 3-step AI users, PFS users and their ability to use a 2-step AI device safely and effectively without intervention by a healthcare provider (HCP) or training prior to use

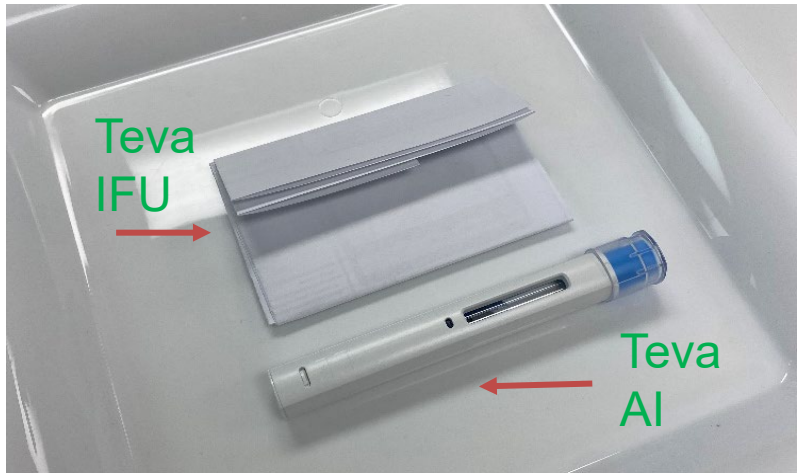
RLD/Reference Device	Indication
3-Step AI 	• Migraines • Arthritis • Lowers LDL
4-Step AI 1 	• Migraines, Cluster headaches • Type 2 diabetes • Psoriasis
4-Step AI 2 	• Arthritis, Crohn's, Psoriasis, UC
PFS with NSD 	• Asthma • Nasal Polyps, Eczema, Dermatitis • Crohn's, Psoriasis, Colitis

Study Structure

GOAL: Explore device crossover and will seek to challenge **the mental models** of experienced 4-step and 3-step AI users and their ability to use a 2 step AI device safely and effectively without intervention by a healthcare provider (HCP) or training prior to use

Study Parameters	Description
Intended User Group, Sample Size	1. Self-administration, 18+ yrs old, Reference Product (RP) experienced 2. Self-administration, 12-18 yrs old, Reference Product (RP) experienced
Study Design	• User's product was substituted at the pharmacy. • Deliver the dose using only the provided IFU. • Threshold Analysis informed design differences for study observation. • URRA informed critical task and helped reduce use risks as low as possible • Root Cause Investigation informed sources of negative transfer.
Data Analysis	• Users were NOT asked to use the reference product • Qualitative data will be collected to assess use errors and their root causes • "Use Error Rates" will not be compared • Benefit/risk is compared with reference product for acceptability

Simulated Study Setting and Tasks



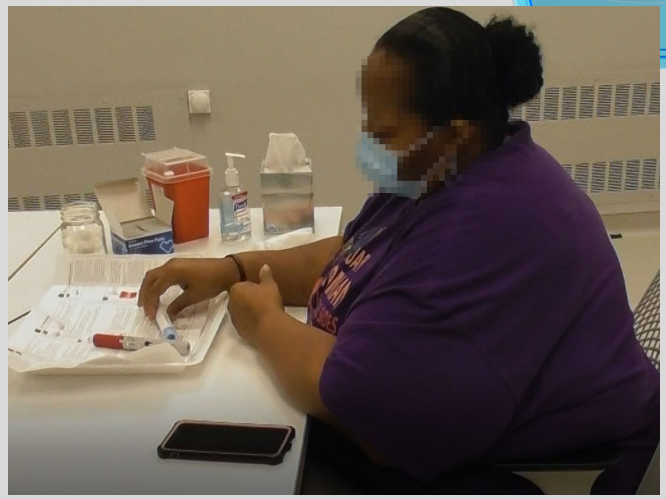
Task	Step	Impact to…
1. Preparation	Visually inspect the AI for physical damages, appropriate medication color, and expiration date.	Safety
2. Inject	Uncap the Pen	Efficacy
	Place the Pen against the skin	Efficacy
	Press and hold down the Pen against the skin; you will hear a click.	Efficacy
	Continue to hold down the Pen until you hear a second click.	Efficacy
3. Dispose	Dispose of the Pen in a sharps bin.	Safety

Simulated Study Setting and Tasks

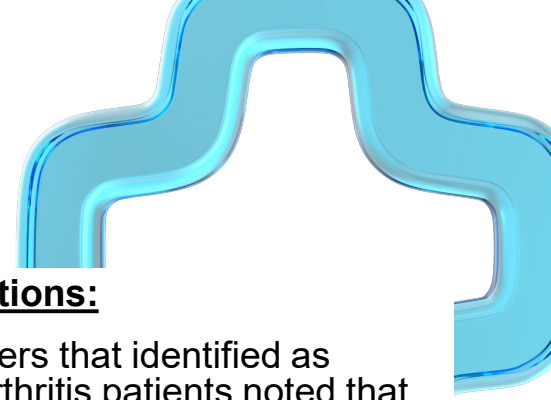
A) User reviews the IFU before use

B) User simulate injection into pad

C) User compares the devices after use.



Successful Case Study



3-step AI

10/20 read IFU

20/20 ✓

4-step AI 1

7/20 read IFU

18/20 ✓

4-step AI 2

16/20 read IFU

20/20 ✓

PFS

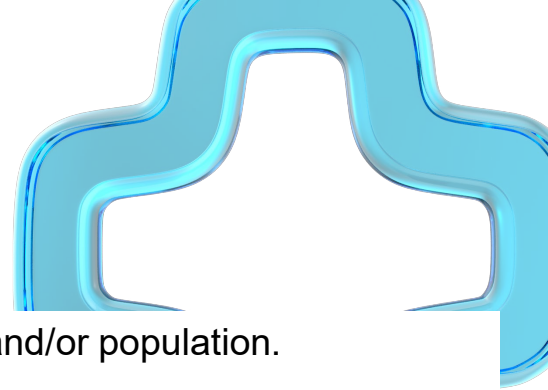
20/22 read IFU

20/22 ✓

Notable Observations:

1. **3-step AI:** Users that identified as rheumatoid arthritis patients noted that is it easier to use an AI without a button due to dexterity requirements for button activation
2. **4-step AI 1:** A viscosity difference between RLD DP and glycerol mimic contributed to an observation of negative transfer for two (2) users; users expected the gx to inject in the same amount of time as their RLD.
3. **4-step AI 2:** 11/20 users preferred not having a button; five stated that the button's presence or absence did not impact the way they used the device; two preferred having a button
4. **PFS with NSS:** Two (2) use errors were observed where users lifted too quickly, causing an incomplete dose. One accidentally activated and immediately realized it, a second did not know that pressure needed to be maintained throughout injection.

Conclusions and Further Discussion



- **Surrogates:** to allow for increased recruiting power, representative of the targeted reference device user interface and/or population.
- **RP Use:** Could artificially reinforce negative transfer and is not analogous to the real-world scenario of pharmacy substitution with the substitutable DDCP → not to be used during study
- **Sample size:** Based on the risk profile of the proposed biosim/gx and the severity of not achieving the primary endpoint of successfully completing a dose.
  - Due to the subjectivity of use errors and the oftentimes infeasibility of the larger sample sizes required by higher primary endpoint success rates, alternative reliability targets are proposed for HF validation studies appropriate for the benefit-risk of that product.
- **Definition of successful performance:** Establishment of an acceptable error rate based on the risk profile of the product, and successful completion of the study would be based on the benefit-risk of the product.
- **Root cause analysis of all use errors:** Focused particularly on **negative transfer** as a root cause and ultimately **the impact on the primary endpoint.**
  - Use errors not associated with negative transfer should be evaluated as to whether they are specific to the use of the proposed biosim/gx or if they could have occurred with the RP.
  - Use error inclusion or exclusion should be justified based on the root cause analysis.

For more information on the study discussed, please see the article published in October 2025 issue of OndrugDelivery: *O'Donel C, Akouka H, DeStefano M, Sanchez-Torres L, "Alternative Approach for Device Substitutability: Human Factors Studies for Generic and Biosimilar Products". ONdrugDelivery,* ***Issue 178 (Oct 2025)****, pp 28–33.*

Thank You.

Questions?