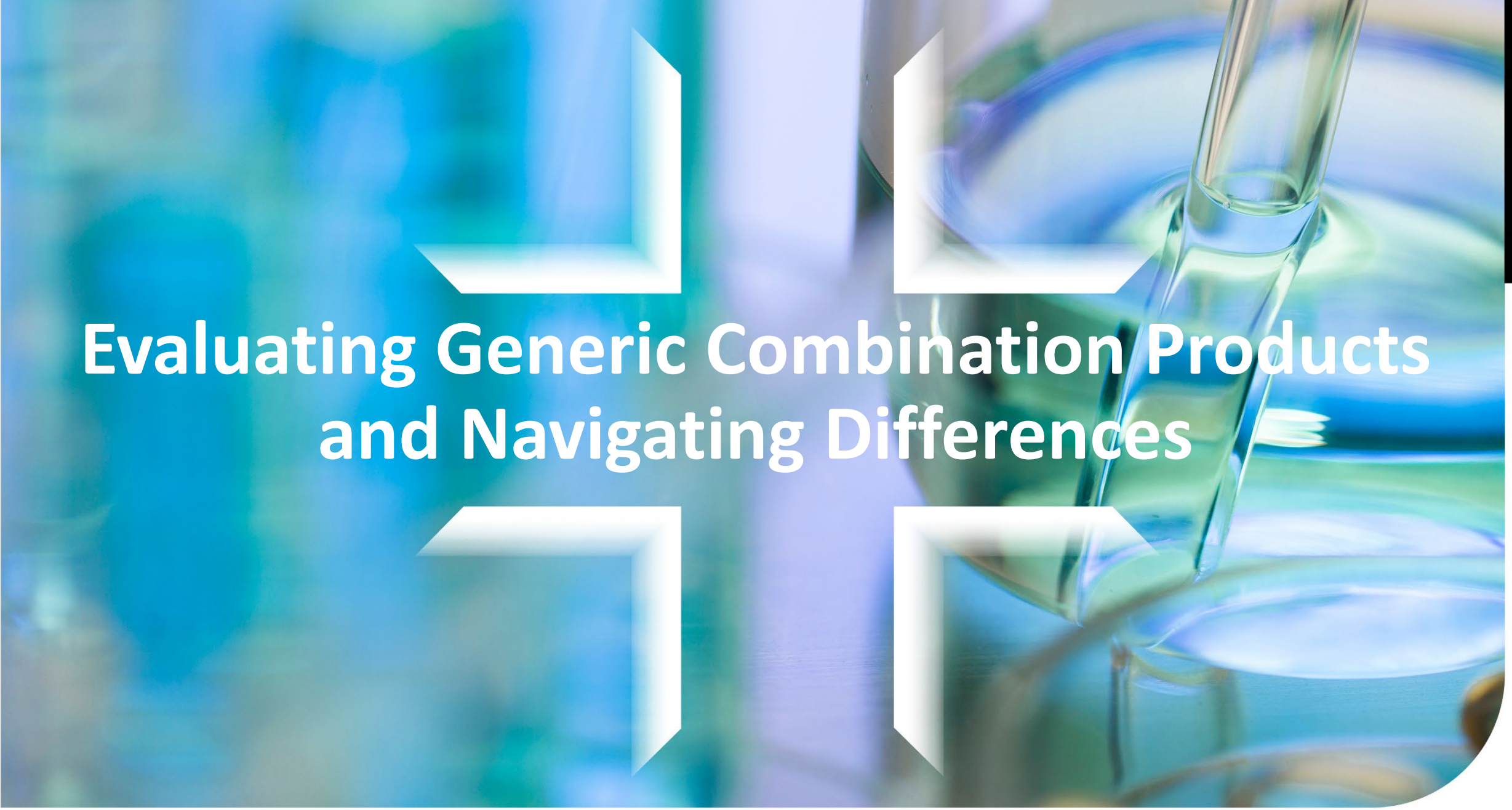

Evaluating Generic Combination Products and Navigating Differences

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Session Objective

Outline the current regulatory framework, scientific data, challenges & opportunities for the evaluation of Generic Drug-Device Combination Product user interface differences

- Understand scientific data that support classification of user-interface differences as minor vs. non-minor and their impact on usability for patients
- Continue the Industry & FDA discussion on opportunities to improve assessment approaches for non-minor differences based on scientific data (e.g. alternative approaches to Comparative Use Human Factors Studies)

Participants

FDA Participants

- **Sharon Ahluwalia,** M.D., Physician, Division of Clinical Review (DCR), OSCE, OGD, CDER, Food and Drug Administration, (Sharon.Ahluwalia@fda.hhs.gov)
- **Andrew Clerman,** M.D., Ph.D., Acting Lead Physician, Division of Therapeutic Performance I (DTP I), ORS, OGD, CDER, Food and Drug Administration (Andrew.Clerman@fda.hhs.gov)
- **Melissa Mannion**, PharmD, JD, Senior Regulatory Counsel, DPD, OGDP, OGD, CDER, Food and Drug Administration (Melissa.Mannion@fda.hhs.gov)

Industry Participants

- **Aparna Dagar,** PhD, RAC, Sr. Director, Regulatory Affairs Fresenius Kabi, (Aparna.Dagar@fresenius-kabi.com)
- **Chris Lamanna,** Ph.D., Head Regulatory Devices Sandoz, (william.lamanna@sandoz.com)

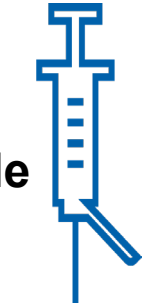
Framework

Delivering safe & functional combination products that are substitutable with the RLD

Device Safety and Functionally Testing: ensuring that the drug product is safely and effectively delivered to the intended site of action

Design Control

- **Safe and consistent fulfillment of performance specs throughout lifecycle**
- **Biocompatibility data (extractable / leachable)**
- **Human factors evaluation**



User interface & substitutability: ensure that intended users can safely use generic device in place of RLD without additional training

Challenge

User interface differences may require challenging HF studies or design change

Comparative Analysis: Evaluation of user interface differences

- Physical comparison
- Comparative task analysis
- Labelling comparison

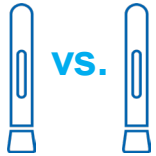
Focus is similarity of critical design attributes - features which may impact safe & effective drug administration

No or only Minor Differences in the user interface

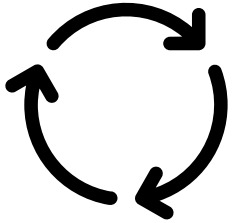
"Other than Minor" Differences

Comparative Use Human Factors (CUHF) study

Design: Stat. comparison of RLD vs. Generic error rates
Participants: divers user groups experience with RLD
Study size: can be large (50-100 patients)
Study length: can be long (6-12 months)
Impact: High / Prohibitive



Design change



Difference Drivers

Device differences can be important to deliver safe state-of-the-art patient friendly features

Differentiation drivers

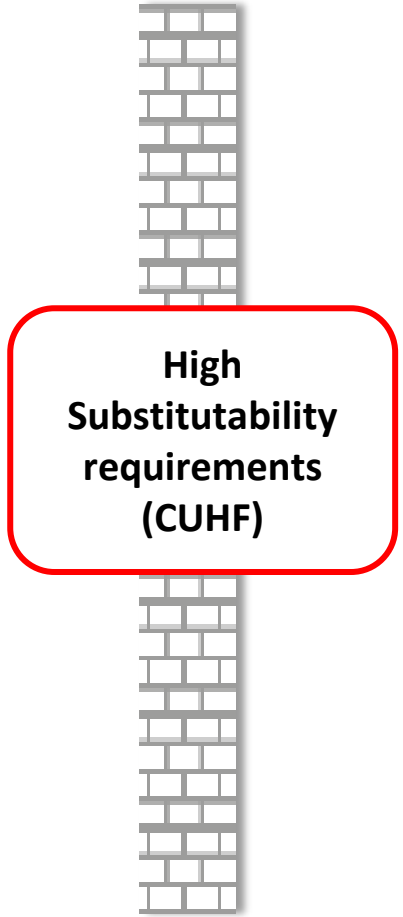
Usability improvements: Wish to improve user interface based on new technology / features

Replacement of unsafe / outdated features: Known use errors with RLD

Leverage platforms: Utilization of device platforms preferred by patients based on real world experience

Unavailable components: Older constituent parts no longer available

Patents: RLD IP may require differentiation for generic market entry



Objective / ideal state

Patient friendly: Device is easy to use and adapted to patient needs

Substitutable: Device can be substituted with RLD without additional training

Safe: Device utilizes state of the art features to maximize safety and address known use errors

Generic Combination Products vs RLD: Navigating Differences An Industry Perspective

Aparna Dagar, PhD, RAC

Sr. Director, Regulatory Affairs

Fresenius Kabi

Substitutability of Generic Combination Product with the RLD

Generic Combination Product Therapeutically Equivalent to the RLD

- ❑ Same clinical effect and safety profile as the RLD under conditions specified in labeling
- ❑ Do NOT need to be IDENTICAL in all respects
- ❑ Expects end-users to be able to use the generic combination product when substituted for the RLD without health care provider intervention and/or additional training

Comparative Analysis (Threshold Analysis)

- ❑ Identify and evaluate user interface differences that can affect end user ability to safely use the product
  - ✓ Physical comparison of device constituent part: critical design attributes
  - ✓ Labeling comparison: IFU, description of device, Full prescribing information
  - ✓ Comparative task analysis-focus on critical tasks
- ❑ Required even when RLD is not a CP, e.g. vial to PFS/IV Bag
- ❑ Minor differences in user interface can be justified

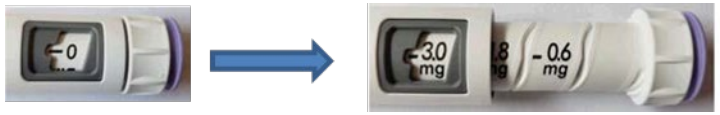
Comparative Use HF study

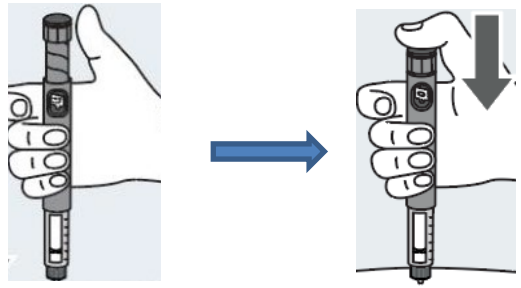
- ❑ If 'other design differences' identified impacting external critical design attributes that involves administration of the drug product
- ❑ Re-design not possible to minimize device differences
- ❑ Assess the design differences between the user interface of the proposed generic CP and RLD to determine clinical risk and safety when proposed drug product is substituted for the RLD.

A Case Study: Lessons Learned

Proposed Product vs RLD	• Pre-filled, variable-dose, multi-use pen injector • Non-emergency use, daily dosing by patient or guardian/caregiver of pediatric patient • Device operated in the same way by dialing to select the dose and pushing to inject the dose
Strategy	• Demonstrated device performance equivalency in regard to functionality, accuracy, and robustness per ISO standards • Formative HF with RLD users-objective and subjective data showing product could be used safely; some participants needed time to get familiar/use it • ***Establish device sameness through a comparative TA and comparative testing of essential design requirements***
PreANDA Meeting Feedback	• Other design differences identified may have an impact on external critical design attributes that involves administration of the product • **CUHF study would be required** to address the differences and assess clinical risk and safety when proposed drug product is substituted for the RLD.

Other Design Differences identified in Pen Injector Product Requiring CUHF





Proposed device: Dose selector barrel/dose button extends out from the main body of the pen

vs

RLD device: dose button remains static in a fixed position

Proposed device: Other doses visible on the dose selector barrel as it extends from pen main body

vs

RLD device: only allows for one dose to be visible in the dose window

Proposed device: dose button requires a dynamic push action to return extended barrel into pen body and deliver dose

vs

RLD device: requires a static push action

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Chain of Events related to CUHF Study

1st Pre-ANDA Meeting Request to ANDA submission: ~24 months

CUHF PROTOCOL

- Paired study with participants using both proposed and RLD pen injectors
- Surrogate participants with similar patient characteristics using RLD equivalent product
- Evaluate critical tasks related to the differing external critical design attributes

Pre-ANDA MEETING

- Justification needed for selected NI margin based on RLD studies
- Comparison only to RLD users and no agreement on use of surrogate patients
  - *If recruitment difficulties during study:* send information on efforts, proposed alternative options and rationale for consideration

Post-Meeting COMMENTS

- Older pediatric user group: no guardian intervention to capture more robust user data
- Primary endpoint of the study is overall use success
- May be necessary to include other critical tasks in the overall use success and not only those impacted by differing external critical design attributes

CUHF Study: "Pilot"

- 42 patients performed in 3 different cities
- Demonstrated -0.30 NI margin and a sample size of 20 subjects would be needed (99.9% power)
- Already evaluated 21 subjects per user group and sufficiently powered to demonstrate proposed pen is non-inferior to the RLD
- Results indicated it is very unlikely (0.01%) that further testing would produce different results.
- Analysis provides substantial data-based evidence to justify other design differences will not impact safe use and no further CUHF testing should be required.

ANDA REVIEW

- Design validation information requested during site inspection and CUHF approach questioned
- CRL with CUHF comments
  - Use of RLD training for new pediatric users
  - No presence of guardian
  - Suggested use of surrogate patients
  - Need to assess deviation from IFU even if not impacting critical tasks and patient's routine practice

Case Study: Real-World Challenges to Consider

Study Design

- Establishing NI margin based on RLD use errors
- Overall use error margin instead of individual critical tasks
- Limited to no published studies on RLD HF data
- Pilot studies to determine NI depletes subjects for subsequent CUHF study

Recruitment of RLD Users

- New patient population, second line treatment
- Other generic products already on market and in use by patients
- Restrictive inclusion criteria, e.g. no presence of guardians for non-emergency products

Costs and Timeline

- Formative/pilot studies to determine CUHF requirements
- Availability and cost of RLD
- Use of 3rd party companies to increase recruitment
- Study performance in multiple cities to recruit sufficient subjects

Opportunity

Scientific data may guide future guidance to address CUHF study design challenges

Challenge

CUHF statistical model: Non-inferiority model applies most stringent error rate margin “d” across all critical use tasks

CUHF study design: Challenges in recruiting, RLD availability and cost

Opportunity

Refine CUHF model to improve assessment of actual patient risk

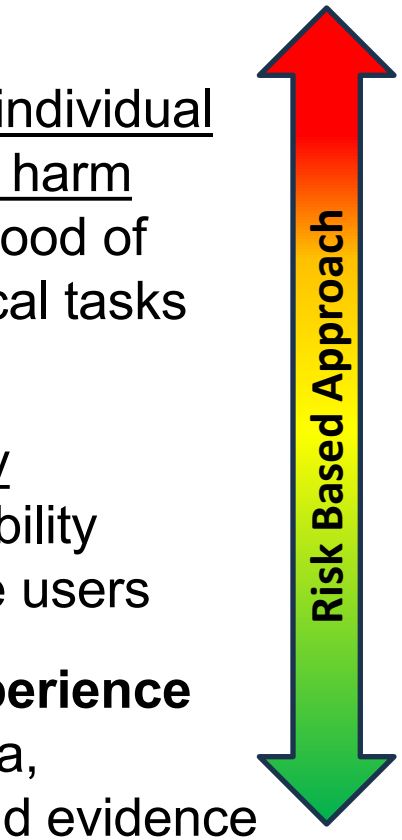
- Application of error margin “d” to individual critical tasks based on severity of harm
- Account for learning effect (likelihood of repeated error) for individual critical tasks

Alternative HF study approaches

- HF study with generic device only
  - Compare generic device usability between RLD users vs. naive users

CUHF waiver based on data & experience

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



Thank You & Questions?