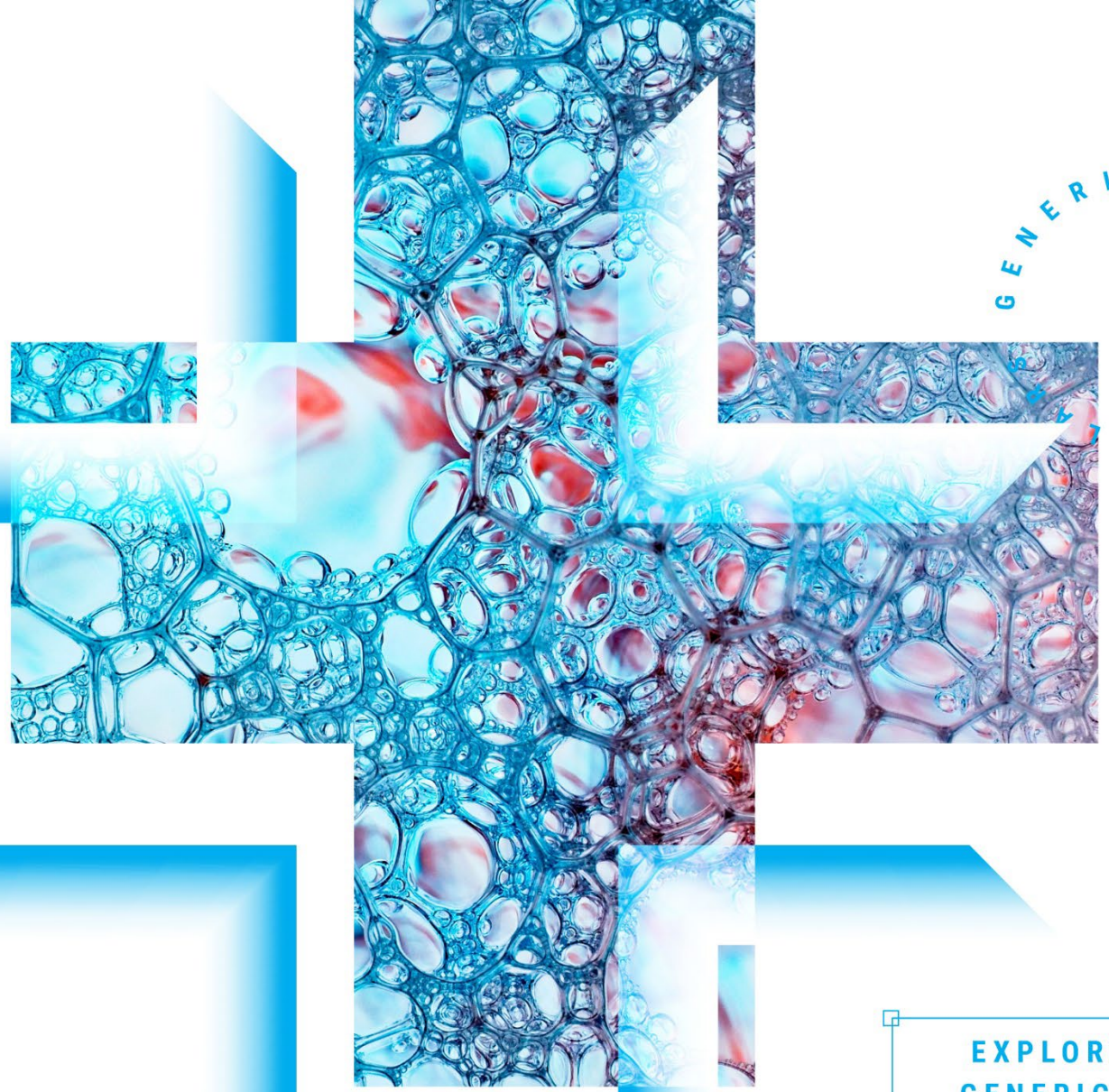
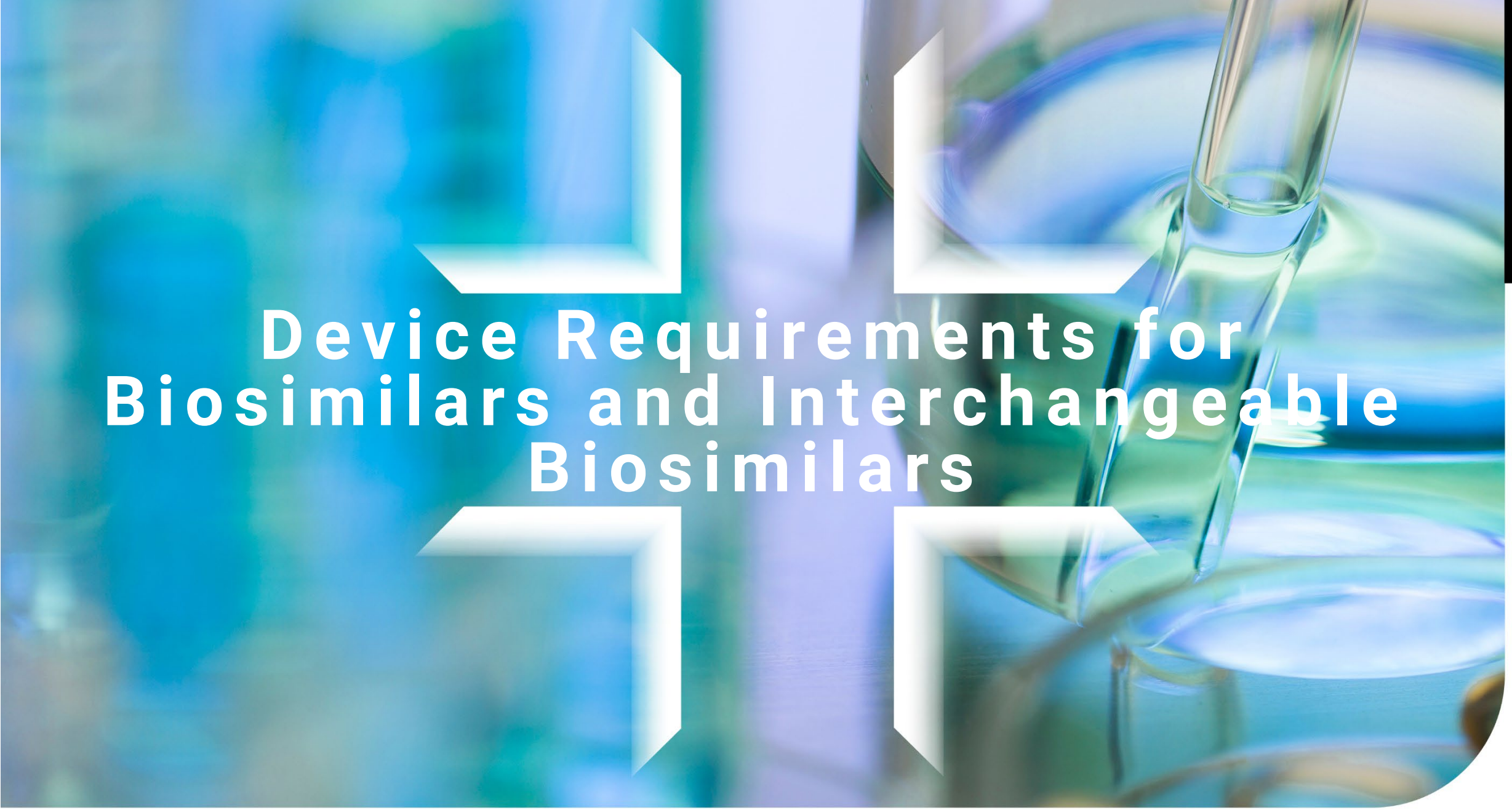


GENERICS AND BIOSIMILARS

GRx+ Biosims™

EXPLORING THE FUTURE OF
GENERICS AND BIOSIMILARS

#GRXBIOSIMS



Device Requirements for Biosimilars and Interchangeable Biosimilars

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Presentation Overview

This session will provide an understanding of current data and outcomes related to device requirements for biosimilars and interchangeable biosimilars and how this might shape future guidances. This session also will provide information on:

- Alternative approaches to Comparative Use Human Factors Studies for those differences that pose no or low risk of differences in use error rates and future guidance
- FDA's perspective on interchangeable biosimilars and devices.
- BSUFA research roadmap efforts that support understanding of user interface differences that will likely lead to differences in use error rates or use success rates

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Focus

What is Similarity and How is it Defined?

What is the Recommended Supporting Data?

CUHFS: How Similarity can be demonstrated?

Challenges with CUHFS: "Other" differences can pose a prohibitive barrier

Opportunities to enable user interface differentiation while ensuring patient safety: A data-driven, risk-based approach

Disclaimer

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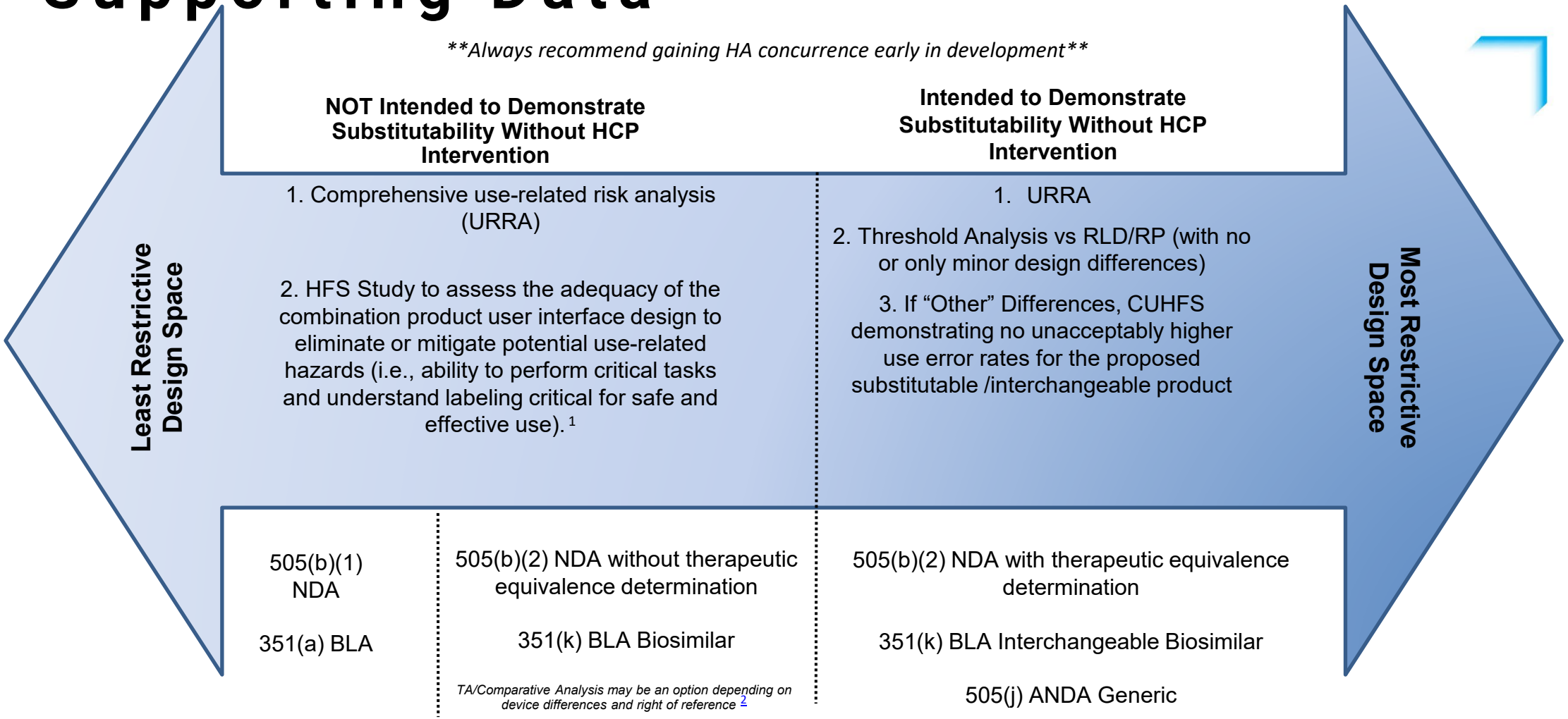
Nothing contained within the presentation is, or should be relied upon as, a promise or representation as to the future and the companies and firms of the presenters expressly disclaims any obligation to update the information if it should change

How is Similarity Defined: Comparisons

- Generic (505(j))
  - Proposed product CAN be substituted for the reference listed drug without additional physician intervention or retraining prior to use
  - Same clinical effect and safety profile when administered to patients under the conditions specified in the labeling
  - Any differences identified should be adequately analyzed, scientifically justified, and otherwise not preclude approval under an ANDA[1]
- BioSimilar (351(k))
  - Highly similar to the reference product (allowing minor differences in clinically inactive components) [3]
  - No clinically meaningful differences with respect to safety, purity, and potency [3]
  - Design differences in the delivery device used with the proposed biosimilar product are permitted if supported by data and provided that the conditions of use do not differ from those previously approved from the reference product[2]
- Interchangeable BioSimilar Product (351(k))
  - Meets minimum requirements for Biosimilar AND
  - Can be expected to produce the same clinical result as the reference product in any given patient[4]
  - The risk in terms of safety or diminished efficacy of switching is not greater than the risk of using the reference product without such switch[4]
  - May be substituted for the reference product without the intervention of the prescribing healthcare provider[5]

[1] https://www.fda.gov/files/drugs/published/Comparative-Analyses-and-Related-Comparative-Use-Human-Factors-Studies-for-a-Drug-Device-Combination-Product-Submitted-in-an-ANDA--Draft-Guidance-for-Industry.pdf
[2] 351(k)(2)(A)(i)(III) of the PHS Act
[3] Section 351(i)(2) of the PHS Act
[4] 351(k)(4)(A) of the PHS Act
[5] Section 351(i)(3) of the PHS Act

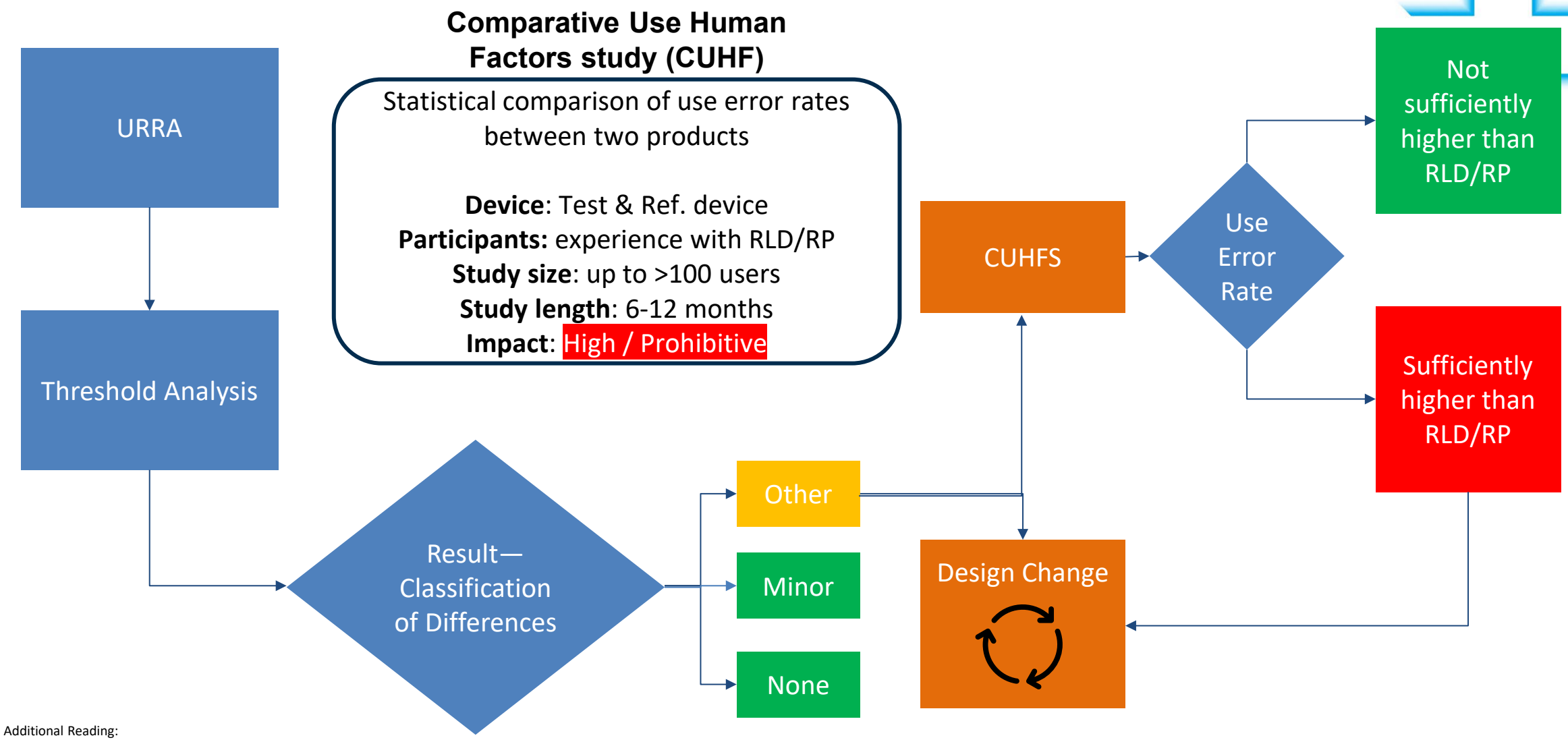
Summary of Recommended Supporting Data



[1] Draft Guidance Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development (February 2016) https://www.fda.gov/files/about%20fda/published/Human-Factors-Studies-and-Related-Clinical-Study-Considerations-in-Combination-Product-Design-and-Development.pdf

[2] Draft Guidance Bridging for Drug-Device and Biologic Device Combination Products (December 2019) https://www.fda.gov/media/133676/download

How Similarity Can Be Demonstrated: CUHFS



Additional Reading:
Draft Guidance Contents of a Complete Submission for Threshold Analyses and Human Factors Submissions to Drug and Biologic Applications Guidance for Industry and FDA Staff (September 2018) https://www.fda.gov/media/122971/download
Draft Guidance Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA: Draft Guidance for Industry (January 2017)
https://www.fda.gov/files/drugs/published/Comparative-Analyses-and-Related-Comparative-Use-Human-Factors-Studies-for-a-Drug-Device-Combination-Product-Submitted-in-an-ANDA--Draft-Guidance-for-Industry.pdf

Opportunities to enable user interface differentiation while ensuring patient safety: A data-driven, risk-based approach

CUHF study: Challenges

CUHF requirements and execution: Limited understanding of FDA expectations for study design and question whether "one size fits all"

- How to define and justify allowable margin *d*
- How to define use error rate of reference product
- How to perform study analysis:
  - Overall use success vs. use error for each task (tailored *d* values for each task depending on criticality?)
- Appropriate statistical powering/sample size
- Challenge for recruitment, reference product availability, cost

CUHF study: Opportunities

FDA guidance: Clear guidance on FDA expectations for study parameters and framework for a risk-based approach if supported by experience / data

- Provide guidance on defining *d,* considering consequence of use errors (severity of harm) and learning effect
- Defined error rate parameters and guidance on endpoints
- Clear expectations for statistical powering and guidance on sample size calculation (e.g. online tool)
- Framework for risk-based approach to CUHF studies if supported by data and experience
  - Alternative study designs, statistical approaches for "lower risk" differences (emergency-use vs. maintenance device)

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

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, originator availability and cost

Opportunity

Refine CUHF model to improve assessment of actual patient risk

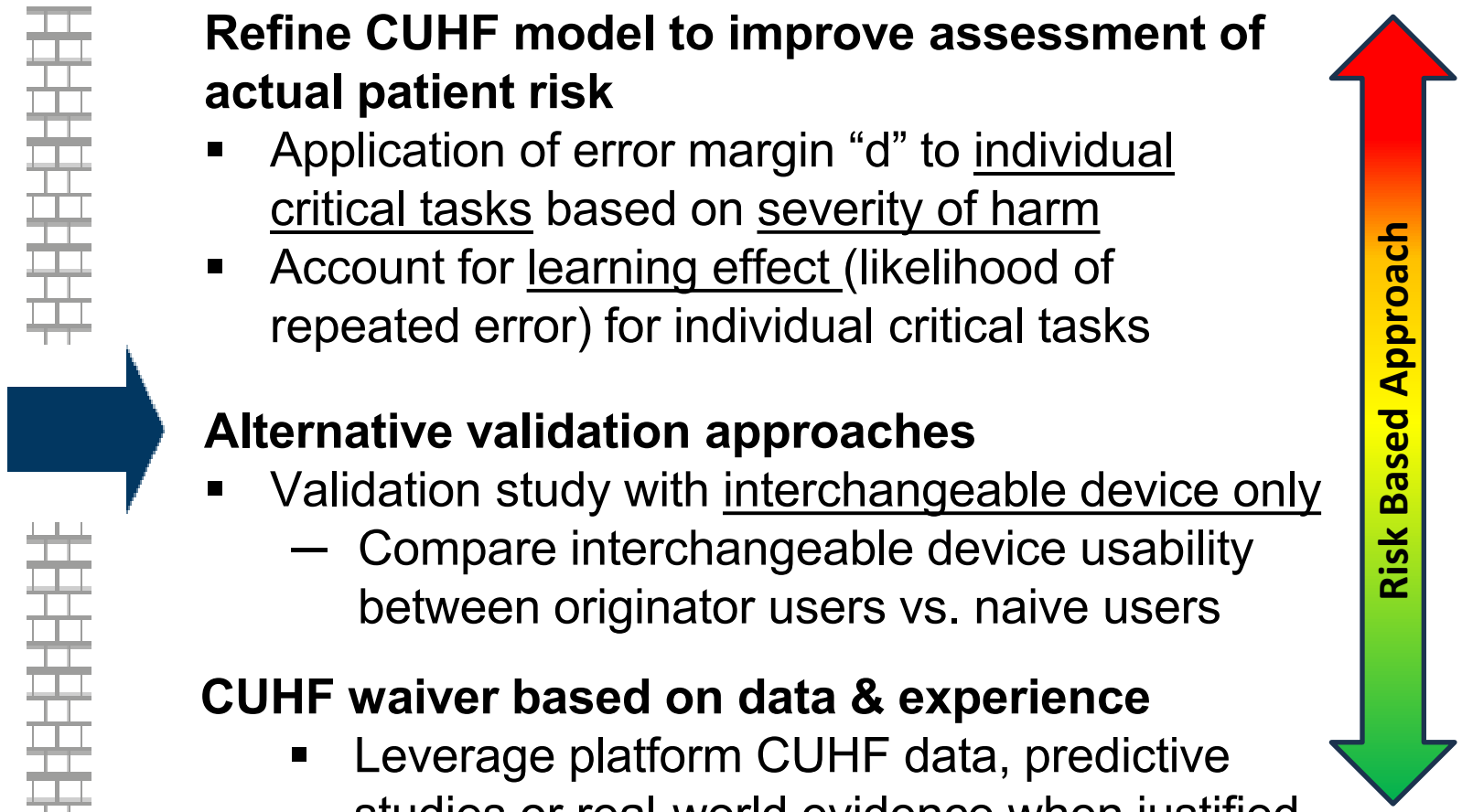
- Application of error margin "d" to individual critical tasks based on severity of harm
- Account for learning effect (likelihood of repeated error) for individual critical tasks

Alternative validation approaches

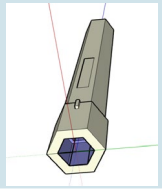
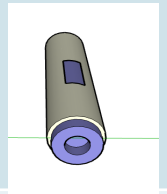
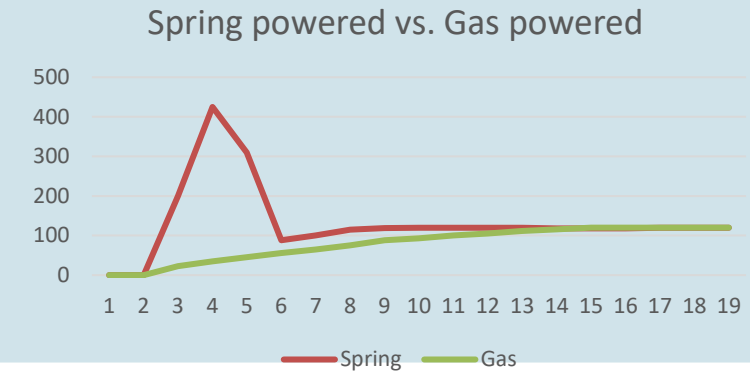
- Validation study with interchangeable device only
  - Compare interchangeable device usability between originator users vs. naive users

CUHF waiver based on data & experience

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



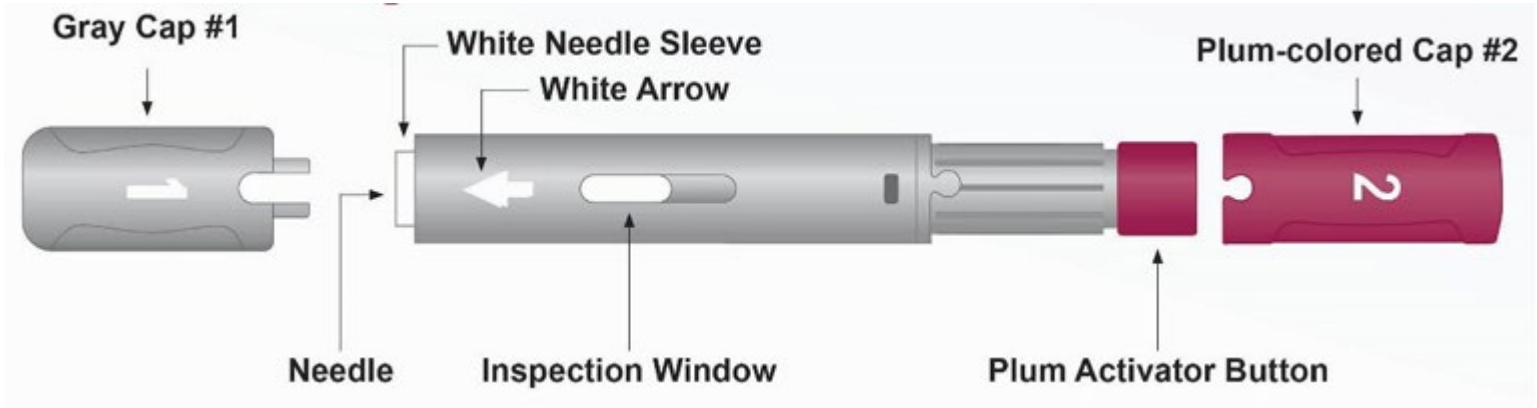
Can these be substitutable devices

	Sample A	Sample B
		
Dosage and Administration	• Patient or caregiver administered • 1 mL of a 10 mg/mL solution (Autoinjector) • Recommended Dose: 10 mg administered as subcutaneous injection as needed every 24 hours • Recommended injection sites: Abdomen, upper thigh or upper arm.	
Task analysis	• Remove cap • Place against injection site • Push to initiate injection • Maintain pressure until injection is complete	• Remove cap • Place against injection site • Push to initiate injection • Maintain pressure until injection is complete
Description	A single dose 1mL 2-step auto injector. Drive mechanism is **spring powered** with Injection Delivery time indicated as “hold for 10 seconds”	A single dose 1mL 2-step auto injector. Drive mechanism is **gas powered** with Injection Delivery time indicated as “hold for 10 seconds”
Energy profile		

Can these be substitutable devices

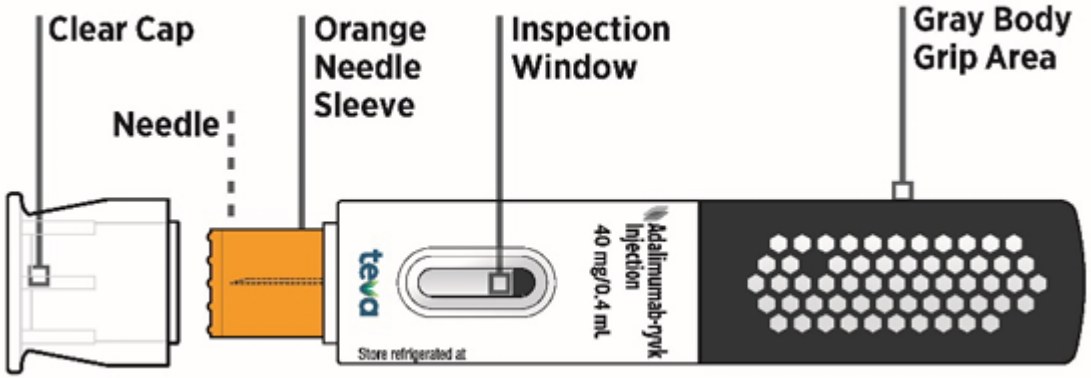
The RP is approved as a 3-Step Auto-Injector.

- Open Cap 1
- Open cap 2
- Press against skin
- Press button to inject



A biosimilar/IC biosimilar applicant seeks approval of an auto-injector with a 2-step Auto Injector.

- Open Cap
- Press against injection site to inject



Is this difference too different?

Soliciting FDA Feedback

- URRA Submission
  - Submit to IND and include specific questions, justification HF validation study is not needed with supporting info
  - BsUFA Commitment Letter Performance Goal:
    - FY2024: 50% in 60 days
    - FY2025: 70% in 60 days
    - FY2026+: 90% in 60 days
- No current BsUFA performance goals defined for review of comparative analyses (industry experience suggests that this review can take up to 11 months)
- HF Validation Study
  - Submit protocol to IND and include specific questions
  - BSUFA Commitment Letter Performance Goal: 90% in 60 days
- BsUFA Meetings
  - Specific questions may be better to discuss during BPD Meetings i.e., specific protocol questions or challenges
  - Various timelines listed in BsUFA Commitment Letter

[1] BsUFA III Commitment Letter: https://www.fda.gov/media/152279/download
[2] Draft Guidance Bridging for Drug-Device and Biologic Device Combination Products (December 2019) https://www.fda.gov/media/133676/download