Comparative Use Human Factors Studies: Challenges and Recommendations

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Regulatory Requirements for Generic Substitutability

History and Statutory Framework

To move forward, sometimes you need to look back!

Our story begins in ***1984 (40 years ago!)*** – Hatch-Waxman Amendments

- ✓ Added section 505(b)(2) and 505(j) to the FD&C Act, which describes abbreviated approval pathways under the FD&C Act for drug products regulated by the Agency.
- ✓ Reflected Congress's efforts to balance the need to "***make available more low-cost generic drugs by establishing a generic drug approval procedure***".

505(j)

- ✓ ANDA - A drug product that is a duplicate of a previously approved drug product, relies on FDA's finding that the previously approved drug product, i.e., the reference listed drug (RLD), is safe and effective.
  - ❖ Contains information to show that the proposed generic product (1) is the same as the RLD with respect to the active ingredient(s), conditions of use, route of administration, dosage form, strength, and labeling (with certain permissible differences) and (2) is bioequivalent to the RLD.
  - ❖ An ANDA may not be submitted if clinical investigations are necessary to establish the safety and effectiveness of the proposed drug product.

Therapeutic Equivalence

- ✓ A scientific premise underlying the Hatch-Waxman Amendments requiring that a drug product approved in an ANDA under section 505(j) of the FD&C Act is presumed to be ***therapeutically equivalent*** to its RLD.

Regulatory Requirements for Generic Substitutability

Therapeutic Equivalence

For an ANDA submitted under section 505(j), the applicant must demonstrate that the proposed generic drug has therapeutic equivalence with the RLD.

- Pharmaceutical Equivalence
  - Same active ingredient(s); same dosage form; same route of administration; same strength
- Bioequivalence
  - The absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study.
- **Expected to produce the same clinical effect and safety profile as the RLD under the conditions specified in the labeling**

Regulatory Requirements for Generic Substitutability

Substitutability Requirements

- The generic and RLD products do not need to be identical as long as the differences do not preclude approval under an ANDA.

- As a rule of thumb, for aspects relating to the drug/device combination product (aside from CMC and bioequivalence requirements for the drug), this means that the labeling should be the same and the ***product must be able to be used by a typical user of the RLD without the intervention of the health care provider and/or without additional training prior to use of the generic combination product.***

Regulatory Requirements for Generic Substitutability

Substitutability Requirements

Comparative analyses are conducted in accordance with the Draft Guidance for Industry, Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA (January 2017) to systematically identify any differences in the user interface between the proposed product and the RLD

- ✓ Labeling comparison: Line by Line similarity analysis of the product information.
- ✓ Comparative task analysis: Step wise task comparison of the use of RLD and generic device to identify differences that could lead to errors.
- ✓ Physical comparison of the delivery device constituent part: Examination and comparison of physical features of the RLD and generic device.

Using comparative analyses, use-related risk assessment, and hazard analyses we can identify and categorize any difference as either no design difference, minor difference, or other difference.

Regulatory Requirements for Generic Substitutability

Navigating Differences in User Interface

No Design Difference

- Ideal scenario – additional data will not be necessary to support approval of an ANDA.

Minor Difference

- Does not affect an external critical design attribute – likely to be viewed as acceptable if data and information is provided demonstrating the differences are in fact minor → No impact to clinical effect or safety profile.

Other Difference

- Impacts an external critical design attribute that involves administration of the product and may impact clinical effect or safety profile.
  - Strongly consider modifying the design of the user interface or design to minimize differences.
  - If present in final design, provide additional data, ***such as data from a Comparative Use Human Factors Study (CUHF study)***, to determine whether the differences identified in the user interface introduce a risk that might impact the clinical effect or safety profile of the generic combination (***e.g., therapeutic equivalence, a scientific premise underlying Hatch Waxman***).

Current Expectations for Comparative Use Human Factors Studies

Objective	Execution	Evaluation and Statistics	Success
Demonstrate that the use error rate, associated with a change in the external critical design attribute for the proposed user interface, does not preclude approval of the proposed product	Allow RLD experienced users to use both the RLD and proposed generic and take objective measures of their performance while undertaking the tasks that are affected by any identified 'other difference'	Study will pre-define 'success' for any use task investigated, other outcomes are considered 'use errors' Performance of the identified tasks is then compared between the RLD and the proposed generic in a statistical non-inferiority test Performance by the users on the RLD is taken as the baseline performance, proposed generic must be non-inferior to RLD performance on assessed tasks Only use errors are statistically analyzed, close calls and use difficulties are not part of the statistical assessment • Close calls and use difficulties do not result in medical consequence and thus excluded • Artefacts (use events that only occur due to this being a study) reduce the sample size on the task being assessed	If the proposed generic is found to be non-inferior to the RLD then this is taken as evidence that while the 'other difference' between the RLD and proposed generic has not been removed via modification of the proposed generic design, the safety profile and clinical effect of the safe and effective RLD have been preserved

Challenges with Current Expectations
HF Principles – The Current Paradigm

The focus of the current CUHF Study guidance is on a binary endpoint – the statistical non-inferiority between RLD and proposed generic

- This focus does not account for the root cause of use errors - a use error can occur for multiple reasons, while an 'other difference' between the RLD and the proposed generic could be responsible for a specific use error, other factors outside of the design differences may account for observed use errors. The current approach presumes that all use errors are caused by 'other differences' only

- Root cause analyses would identify negative transfer between RLD and proposed generic device. **Negative Transfer is defined as the interference of previous knowledge with new learning, where one set of events could hinder (adversely affect)/etc.... performance on related tasks**

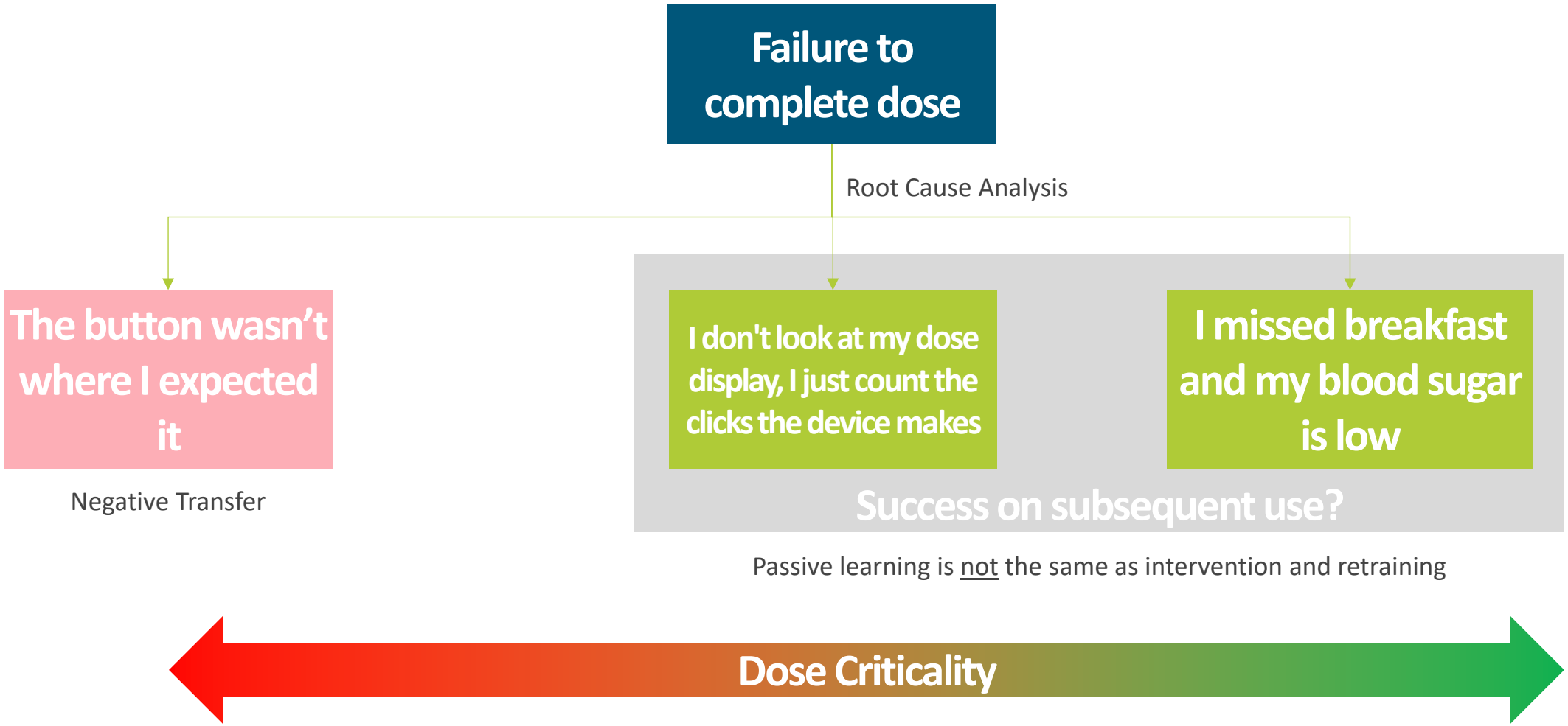
- The exclusion of use events such as close calls and use difficulties also excludes considerations of the root cause analyses of these use events, similar to use errors - these may or may not be linked to the 'other differences' identified between the RLD and the proposed generic

Challenges with Current Expectations
HF Principles – The Current Paradigm

No consideration of RLDs that are used for chronic conditions → repeated use of a device with 'other differences' will result in the user adapting to device differences, whereas the CUHF Study is a 'one and done' – the human ability to learn and adapt is not considered

No consideration of new users that will adopt the treatment as the generic comes onto the market, lowering price and increased availability will lead to new adopters of the treatment that are not considered under the current paradigm

A Use Error is NOT a Data "Point"



Challenges with Current Expectations

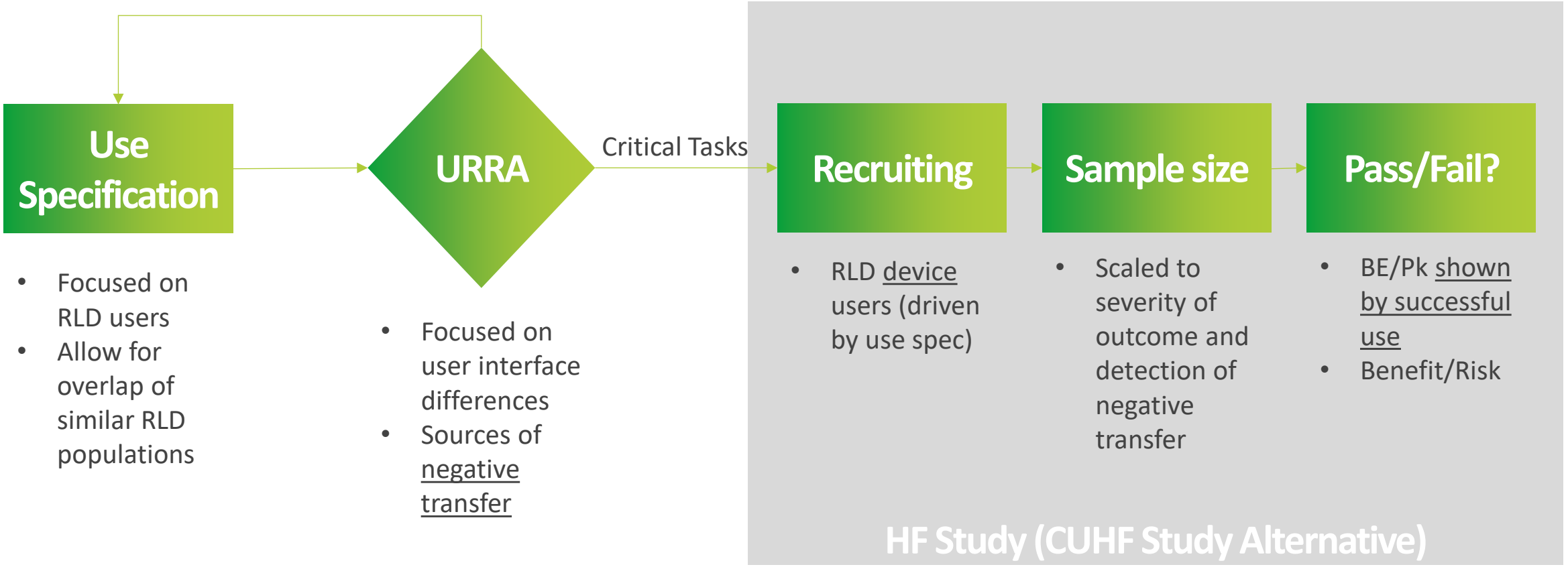
Statistical Implementation (Creating a Robust Statistical Analysis Plan)

- Calculation of non-inferiority margin requires information on the RLD that is not available - generic manufacturer must investigate RLD performance prior to conducting the CUHF Study
- Alignment between the agency and generic manufacturer on non-inferiority margin and end points has been particularly tricky → Requires numerous attempts to align with the agency (time/resource)
- Criticality of the drug and context of use not considered (e.g., chronic condition maintenance vs emergency recovery) - Use errors are not weighted due to their clinical consequences

Practical Implementation

- CUHF Study guidance leads to very large recruitment targets - there are likely to be diminishing returns on increased sample size - 'new' use errors are unlikely to be detected by increasing the sample size
- Agency has required recruitment of indicated but non adaptive user groups (e.g., a medication may be indicated for adolescent self administration, but may not be adapted by adolescents)
- Agency has excluded the use of surrogate participants that were using a non-indicated drug in the correct (RLD) device – real life experience gained on the RLD device was excluded from CUHF Studies

Alternative Study Design Consideration
IEC 62366 Applied to Gx



Alternative Study Design & Data Analyses Considerations

- Target recruitment of RLD users to simulate a high-risk scenario where the user has the prescription changed
- Focus on use of proposed generic device by RLD **device** users
- Do not artificially reinforce negative transfer through the use of RLD
- Focus analysis of results on areas of negative transfer between RLD and proposed generic
- Sample sizes, scaled to safety profile
  - Smaller (e.g., 15-20), failure to complete the dose may result in injury that is not life threatening
  - Moderate (e.g., 20-50), failure to complete the dose may result in injury that is life threatening
  - Larger (e.g., 50-100), failure to complete the dose may result in death
- Emphasis on route cause analysis of use errors, use difficulties and close calls rather than statistical analyses of use errors
- Pass/fail criteria
  - 10-15% failure to complete the dose may be OK depending on the root cause and clinical impact and safety profile
  - Successfully completing the dose on subsequent use may be OK depending on the clinical impact and safety profile
  - Bioequivalence through successful use measured by benefit/risk

Successful Case Study

Scenario: Users reference product was replaced with a 2-step AI and a mock IFU

3-step AI

20/20 ✓

4-step AI

18/20 ✓

4-step AI

20/20 ✓

PFS

20/22 ✓

Recommended Areas of FDA Research Related to Comparative Use Human Factors Studies

- #1 – Understanding of how users adopt techniques for new medical devices over time
- #2 – Understanding of what devices have been approved for multiple indications and how different use cases have been afforded by the same design
- #3 – Understanding of indication vs. adaptation gap
- #4 – Understanding of which areas of medicine are likely to have high incidence of non-indicated drugs being prescribed

Recommended Areas of FDA Research Related to Comparative Use Human Factors Studies

- #5 – Understanding of use errors caused by negative transfer vs use errors caused by device naivete - which group are most at risk from the introduction of a new combination product
- #6 – Sample size – different device types, conduct large sample size test to understand normal use error rates
- #7 – Focusing available use error data on currently marketed products and making available to industry
- #8 – Investigate how a more traditional qualitative human factors study design with appropriate root cause analyses of use events may be appropriate to provide evidence of device comparability/substitutability

Conclusion

- ✓ In the spirit of the Hatch-Waxman Amendments 40 years ago, the goal is still to ***make available more low-cost generic drugs…***
- ✓ Availability of high-quality generic drug-device combination products is essential for making important drug treatment options more accessible to more Americans, but there are ***challenging regulatory and scientific obstacles that hinder the development and timely approval.***
- ✓ CUHF Studies, as they are currently constructed, are prohibitive to generic drug availability and alternative considerations are needed.
- ✓ The human factors expertise needed to facilitate timely approvals already exists within FDA and industry → Let's get "back to basics" → the evolution of IEC 62366 fit for purpose for substitution (not the revolution that the current CUHF Studies are).

✓ **ALTERNATIVE STUDY DESIGNS AND DATA ANALYSES CONSIDERATIONS COULD BE THE KEY TO UNLOCKING CRITICAL GENERIC DRUG-DEVICE COMBINATION PRODUCT AVAILABILITY!**

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Thank You!!!


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