Drug-Device Combination Products: Methodologies for User Interface Evaluation

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Learning Objectives

- Provide the key principles for comparative analyses (CA) and understand key CA definitions
- Discuss FDA's experience with CAs
- Explain the human factors research being conducted by FDA
- Describe the taxonomy and how to implement it

Drug-Device Combination Products: Methodologies for User Interface Evaluation - Part 1

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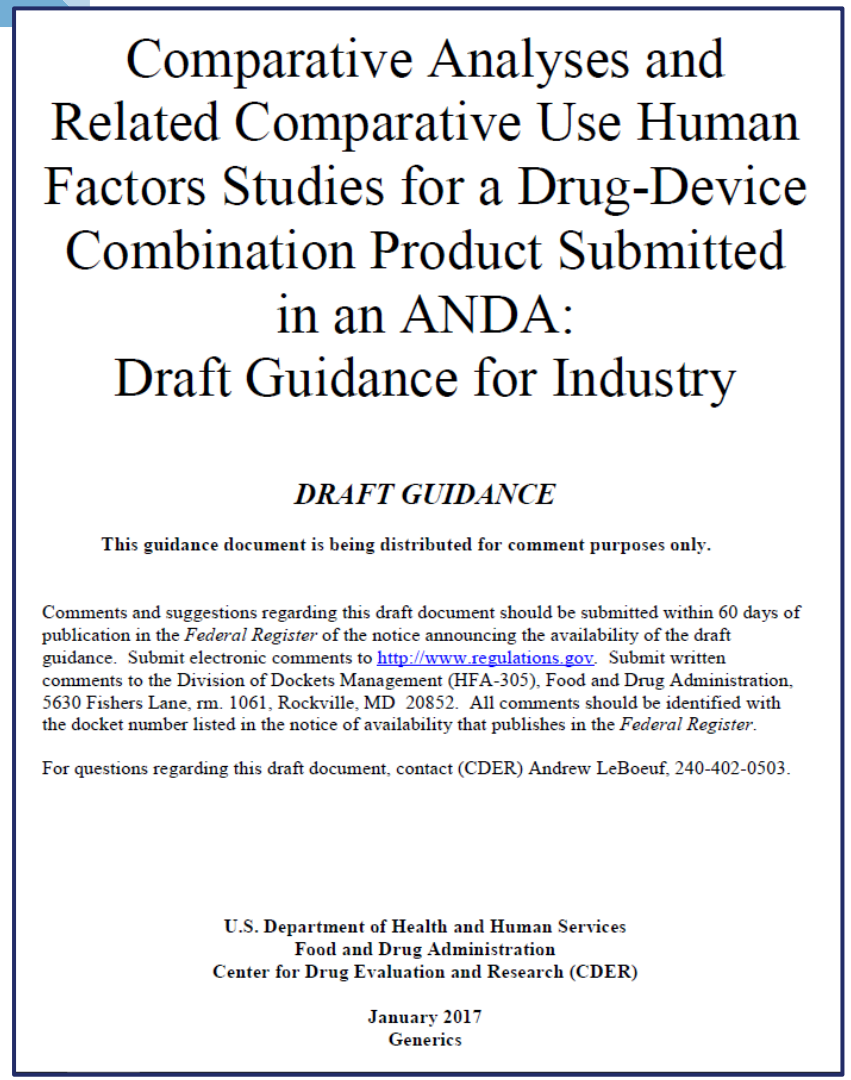
Generic Drug-Device Combination Products

- **Therapeutic equivalence**
  - "... can be expected to have the *same clinical effect and safety profile* when administered to patients under the *conditions specified in the labeling.*"
- **Same expectations** apply for generic drug-device combination products
  - FDA considers whether end-users can use the generic combination product when it is substituted for the reference listed drug (RLD)
    - Without the intervention of the healthcare professional *or*
    - Without additional training prior to the use of the generic combination product
- Generic and RLD products do not need to be identical
  - As long as the differences do not preclude approval under an abbreviated new drug application (ANDA)

Draft Comparative Analyses Guidance



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Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA: Draft Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.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be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance.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

Labeling comparison: FDA recommends a side-by-side, line-by-line comparison of the full prescribing information, instructions for use, and descriptions of the delivery device constituent parts of the generic combination product and its RLD.

Comparative task analysis: FDA recommends that potential applicants conduct a comparative task analysis between the RLD and the proposed generic combination product.

Physical comparison *between RLD and generic device constituent parts:* FDA recommends that the potential applicant of the proposed generic combination product acquire the RLD to examine and compare (e.g., visual and tactile examination) the physical features of the user interfaces of the RLD and proposed generic products.

Access at:
https://www.fda.gov/regulatory-information/search-fda-guidance-documents/comparative-analyses-and-related-comparative-use-human-factors-studies-drug-device-combination

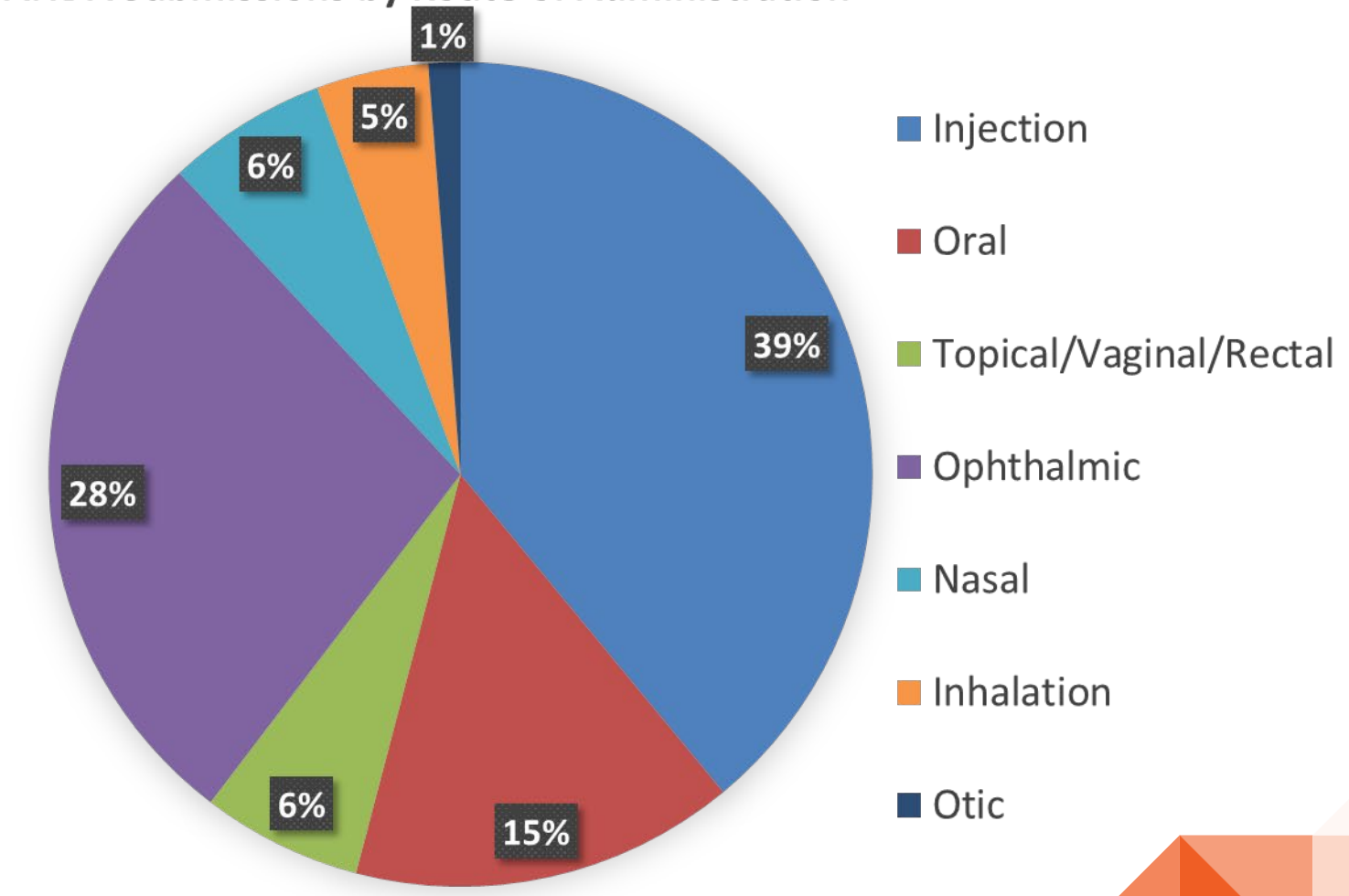
Key Definitions

User Interface (UI)	• All components of the product with which a user interacts • Includes delivery device constituent part and any associated controls, displays, product labeling, and packaging
Critical Task	• A user task that, if performed incorrectly or not performed at all, would or could cause harm to the patient or user, where harm is defined to include compromised care
External critical design attribute	• A feature that directly affects how users perform a critical task that is necessary in order to use or administer the drug product

Comparative Analyses

January 2018-December 2023

Over 1000 Comparative Analyses submitted for ANDAs



Comparative Analyses Outcomes

- No Design Difference
- Minor Design Difference
  - If the difference in the user interface of the proposed generic combination product, in comparison to the user interface of the RLD **do not affect** an external critical design attribute
- Other Design Difference
  - If any aspect of the CA suggests that 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 on which a user would rely to perform a critical task

Other Design Differences

- ***A product with an "other" design difference may be approved as an ANDA but may require further evaluation***
  - What is the risk if the anticipated error occurs?
  - Does it impact the proposed generic having the *same clinical effect and safety profile* as the RLD?

Assessed based on the RLD

& on an ANDA-specific basis

Other Differences- Unacceptable

Comparative Analyses

January 2018-December 2023

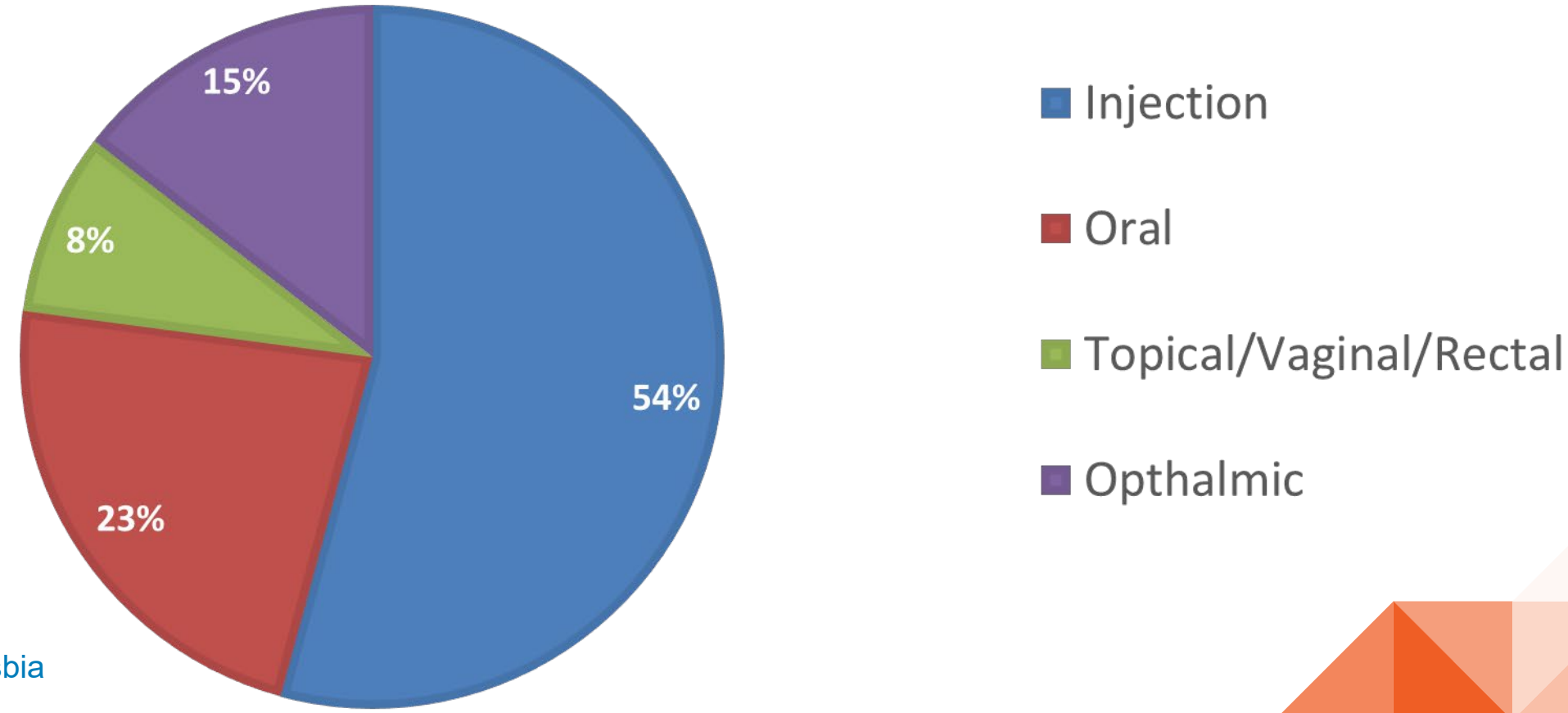
83 "Other" differences-Unacceptable

- Deficiencies communicated throughout the review cycle
- Complete Response Letter sent if issue(s) can not be resolved
- 10% of CA outcomes

Other Differences- Unacceptable

Comparative Analyses

January 2018-December 2023



Options to Address "Other" Design Differences

- Modify the user interface design to minimize differences
- Provide additional data/information
  - Support/justify that the difference will not alter overall risk profile when generic substitution occurs
  - Additional data examples: in vitro study, a comparative use human factors (CUHF) study
- Ongoing Research → to be continued in Part 2

U.S. FOOD & DRUG ADMINISTRATION

Drug-Device Combination Products: Methodologies for User Interface Evaluation

Part 2

Betsy Ballard, MD
Medical Officer
DTP 1/ORS/ OGD

Poll Question

Have you submitted and /or conducted a Comparative Use Human Factors Study?

A. Yes, I have

B. No, I have not

C. I'm not sure what a Comparative Use Human Factors study is

Timeline

2012
GDUFA program established, and Office of Generic Drugs (OGD) becomes a CDER Super-Office; GDUFA research program established

2017
Publication of Draft Guidance on Comparative Analyses & Related CUHF Studies for a DDCP Submitted in an ANDA;

GDUFA II begins.

2020
OGD's Office of Research and Standards establishes Device Evaluation Team to support pre-ANDA comparative user interface reviews and research for DDCPs

2021
Grant Request for Applications issued, submissions reviewed, awards made for FY22 funding to support

Research Grants

- User Interface Design for Generic vs. Reference Listed Drug (RLD) Combination Products
  - Battelle Centers/Public Health Research and Evaluation
- Development of a Combination Product Taxonomy and Comparative Human Factors Testing Method for Drug-Device Combination Products Submitted in an ANDA
  - University of Detroit

RLD: reference listed drug

User Interface Design for Generic vs. RLD Combination Products

- Aim 1 – Develop enhanced methods for threshold analysis and categorization of user interface differences
- Aim 2 – Establish effective methods for assessing “Other” design differences

Outcomes

- No outcomes to report

Development of a Combination Product Taxonomy and Comparative Human Factors Testing Method for Drug-Device Combination Products Submitted in an ANDA

- Aim 1 – Develop a body of knowledge of key stakeholder perspectives and existing strategies for assessing user interface (UI) designs
- Aim 2 – Develop a visual taxonomy to systematically analyze combination product UI design attributes
- Aim 3 - Develop a method for the comparative analysis of a proposed generic DDCP and its RLD

Taxonomy Development

- Taxonomy of Design – a method for organizing specific concepts and creating a vocabulary for those concepts
- Want to link the design feature to task(s) and risk

Milestones

- Aim 1:
  - Interviews completed and a literature search performed
  - Publication
- Aim 2:
  - Taxonomy was developed
  - Taxonomy was validated
  - Case report using the taxonomy is being developed
- Aim 3 – Not completed

Process for Developing the Taxonomy

1 - Combination Product Category

Inhaler, auto-injectors, etc.

3 - Use Error Analysis

Identification of known use error

5 - Link to User Interface Elements

Identification of design interface / component linked to identified risk

2 - Task Analysis

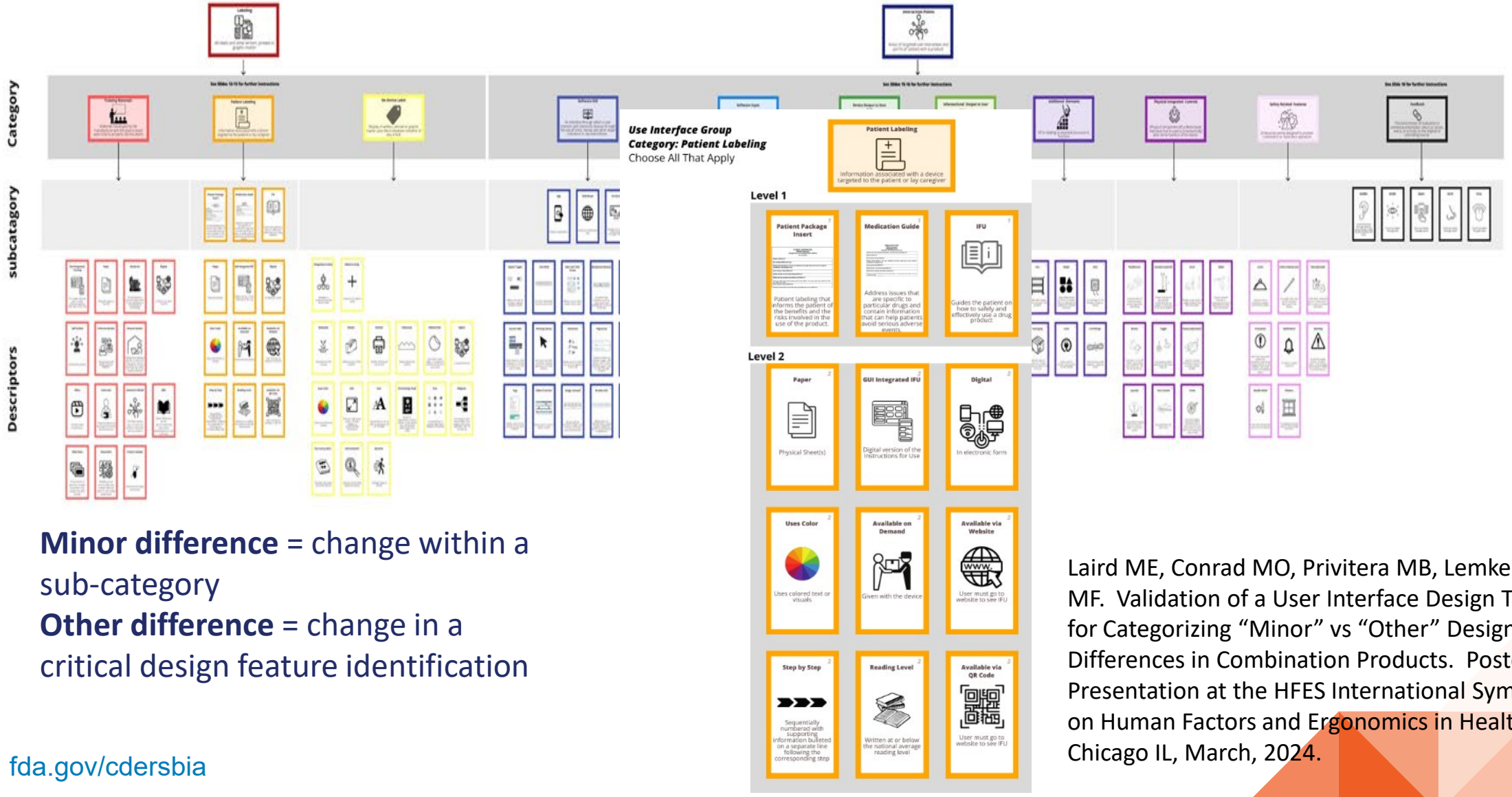
Detailed steps of task/sub-tasks including manual and mental activities necessary to use product

4 - Risk Assessment

Identification of potential hazards and consequences

Laird ME, Conrad MO, Privitera MB, Lemke ME, Story MF. Validation of a User Interface Design Taxonomy for Categorizing "Minor" vs "Other" Design Differences in Combination Products. Poster Presentation at the HFES International Symposium on Human Factors and Ergonomics in Healthcare, Chicago IL, March, 2024

Medical Device Taxonomy



Minor difference = change within a sub-category

Other difference = change in a critical design feature identification

Laird ME, Conrad MO, Privitera MB, Lemke ME, Story MF. Validation of a User Interface Design Taxonomy for Categorizing "Minor" vs "Other" Design Differences in Combination Products. Poster Presentation at the HFES International Symposium on Human Factors and Ergonomics in Healthcare, Chicago IL, March, 2024.

Medical Device Taxonomy Spreadsheet

Developed a spreadsheet which incorporates each task/subtask

Walks user through a series of questions that delve into the hierarchy

	A	B	C	D	E	F	G	H
25	Task Analysis			User Interface				
26	Task #	Task	Sub Task	Group	Category	Subcategory & Descriptors	Feedback	Comments
50	3	Take Blood Pressure	hold start/stop button to turn on and pressurize	Labeling	Training_Materials	Paper	Visible	including photo
51				Labeling	On_Device_Label	Printed	Visible	orange button says start/stop
52				Labeling	Other		Visible	instructions on side of box
53				Interaction_Points	Physical_Integrated_Controls	Pushbutton	Visible	orange stop/start button
54				Interaction_Points	Physical_Integrated_Controls	Pushbutton	Audible	long tone
55			Sit still and allow device to pressurize	Labeling	Training_Materials	Paper	Visible	Instructions in the owner's manual 15 including photo
56				Interaction_Points	Informational_Output_to_User	Real_Time_Information	Visible	pressure reading
57				Interaction_Points	Informational_Output_to_User	Patient_Self_Monitoring	Visible	shows heart blinking along with heart rate
58			Once done pressurizing, remove cuff from arm	Interaction_Points	Fundamental_Elements	Other	Haptic	when pressure releases in the cuff it makes sense to remove it

Laird ME, Conrad MO, Privitera MB, Lemke ME, Story MF. Validation of a User Interface Design Taxonomy for Categorizing "Minor" vs "Other" Design Differences in Combination Products. Poster Presentation at the HFES International Symposium on Human Factors and Ergonomics in Healthcare, Chicago IL, March, 2024.

Results

- Proposed determination report

A "minor" design change must	An "other" design change may
✓ Link to a non-critical task	✓ Link to a critical task
✓ Not add new or increase potential harm	✓ Add new or increase potential harm
✓ Not add or eliminate a task(s)/subtask(s)	✓ Add or eliminate a task(s)/subtask(s)
✓ Not change the action required to complete the task	✓ Change the action required to complete the task
✓ Fall within the same descriptor card within a design taxonomy	✓ Fall within a different descriptor card on a design taxonomy than the RLD design feature

Conrad, M.; Research team discussion. July 2024

Future Directions

- Develop the taxonomy as a web-based tool
  - Use results to determine if design differences are minor or “other”
- Apply the taxonomy in a larger study
  - Compare RLD to generic
  - Test across a wide range of users
  - Continue revising and updating the taxonomy

Ongoing Research

- **IDIQ** (Indefinite Delivery Indefinite Quantity)
  - Conduct a Comparative Use Human Factors Study
  - Potential to evaluate data with different statistical methodologies

Summary

Taxonomy is a powerful tool for user interface (UI) evaluators to classify design differences

- Provides a common language
- Can assess the level of risk associated with the design differences
- Needs to be implemented in larger study of the comparative process

Summary

Office of Generic Drugs continues to fund human factors research

- IDIQ contract went out in May 2023
  - Devices being selected
  - CUHFS being developed
- Broad Agency Announcement will be announced November for FY 2025

Resources

Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug Device Combination

Human-Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development

Application of Human Factors Engineering Principles for Combination Products

Applying Human Factors and Usability Engineering to Medical Devices

Safety Considerations for Product Design to Minimize Medications Errors

Non-Inferiority Clinical Trials to Establish Effectiveness

Bridging for Drug-Device and Biologic-Device Combination Poducts

Challenge Question #1

Which of the following is true regarding "other" design differences:

A. A comparative use human factor study (CUHF) is always required

B. The design difference may impact a critical task

C. They preclude approval under an abbreviated new drug application (ANDA)

D. The applicant must modify the design to minimize difference

Challenge Question #2

Which of the following are current research projects the FDA is conducting?

A. Taxonomy development

B. User Interface Design for Generic vs. RLD Combination Products

C. Conduct a Comparative Use Human Factors Study

D. No current research in this space