Generic Drug-Device Combination Product Research – focus on comparative device user interface assessment and how differences impact users

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Topics

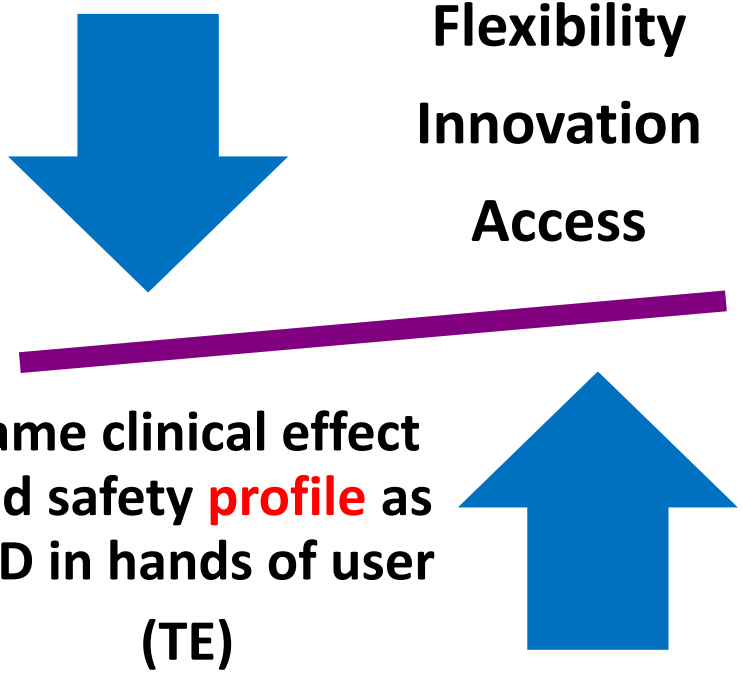
- Known generic drug industry challenges with development of drug-device combination products (DDCPs) related to user interface differences
- FDA-supported research about comparative user interface assessment and the role of published outcomes
  - Attitudes and perceptions of generic substitution of complex DDCPs – findings from focus group studies
  - Current grant-based research
  - Plans for future contract-based research

Known industry challenges with DDCPs

- Controlling cost and avoiding violation of patent protections while….
- Choosing or developing a device user interface viewed as substitutable for the reference listed drug (RLD)
- If user interface differences may affect external critical design attributes, how to justify that the difference(s) will not lead to higher rate of user errors compared to RLD
  - What types of data/information can answer this question other than a comparative use human factors (CUHF) study?
  - If design a CUHF study, challenges identifying existing data to justify choice of noninferiority margin and sample size

FDA's Balancing Act: Finding the Sweet Spot

- Optimize access to affordable, high quality generic drugs for the American public while….
- Ensuring therapeutic equivalence (TE) between RLD and its generics



Human Performance, Human Factors (HF), and Generic Substitutability

What we know

- In most states, generic substitution can occur at the pharmacy without prior notification of patient or prescriber
- Should require no additional training of user (beyond that provided for RLD)
- If difference may affect an external critical design attribute or adds a task, data must show no increase in user error rates

What we want to know

- Which types of task differences can users navigate without an increase in user error?
  - Little published data
  - CUHF study outcomes submitted to FDA not published
  - How can existing anthropometry, existing comparative HF data, and other non-CUHF studies be used to inform this space?
- How is successful generic substitution impacted by patient/caregiver perceptions of and attitudes about generic substitution of complex drug-device combination products?

GDUFA Research Program and DDCPs

- **Current Goals:**
  - Completed patient and caregiver attitudes towards and perceptions of generic drugs and generic substitution of complex DDCPs.
  - Develop human factors based tools and methods for determining whether a user interface difference between a proposed generic and its RLD is a "minor design difference" vs. "other design difference."
  - Identify types of study data/information, other than those from CUHF studies, that could justify that an "other design difference" is unlikely to increase the risk for user error.
  - Conduct CUHF studies funded by FDA that answer questions about whether certain user interface differences increase risk for use error and publish data.

A Formative Research Study to Understand the Impact of Generic Drug-Device Substitutes for Various Patient and Caregiver Populations (HHSF223201810113C)

- Contract awarded 09/21/2018 to RTI International. Completed 04/30/2023.
- Purpose:
  - Advance FDA's understanding of patient and caregiver attitudes toward drug-device combination product (DDCP) substitution.
  - Learn how differences in design and usability features impact patients' views of product quality, efficacy, device usability.
  - Build an evidence base to inform policy.
- Qualitative study using focus groups (in-person and remote) with journey mapping exercise

Two populations, one study design

- Two study populations:
  - Dry powder inhaler users with asthma and/or chronic obstructive pulmonary disease (COPD) (adult and adolescent patients only)
  - Epinephrine auto-injector (EAI) users (caregivers and adult and adolescent patients)
- Segmented recruitment of adult and adolescent (12-17 yrs) patients and caregivers (EAI study only)

- Focus groups
  - All in-person for DPI groups
  - Half in person, half remote for EAI groups due to COVID
- Focus group structure
  - Pre-group questionnaire
  - Generate discussion about overall perception of generic drugs
  - Journey mapping exercise:
    - 3-step potential real-life scenario relevant to participants

What is….Journey mapping?

- Used in market research to understand consumer perceptions and decision-making.
- Adapted to better understand how patients navigate complex systems and make health decisions.
- Potential relevant scenario presented to participants – three parts:
    1. Participant orders a refill for their prescription brand DPI or EAI
    2. Participant picks up the prescription and receives a generic DPI or EAI for the first time instead of their current brand product
    3. Participant uses the generic DPI or EAI for the first time
        - During Steps 2 and 3, participants had access to brand and generic product devices (drug removed) or trainers to handle and manipulate.

DPIs: Brand and Generic Products

Brand (RLD)

Generic

- 4 groups of adult DPI users (N = 36)
  - 80.6% with asthma diagnosis
  - 22.2% with COPD diagnosis
  - 69% trained before DPI use
- 1 group of 4 adolescent DPI users
  - 2nd group cancelled due to COVID
  - 50% trained before DPI use

Ray SE, Boudewyns V, Davis C, Tzeng JP, Srivastava I, Oguntimein O, et al. Patient perceptions of switching to a generic dry powder inhaler – increased understanding through journey mapping. Int J Chron Obstruct Pulmon Dis. 2022 Aug 6;17:1751-1768.

EAIs: Brand and Generic Products

- Brand (RLD)

- Generic

- 8 focus groups (4 in-person; 4 remote due to COVID)
  - 3 caregiver groups (N = 21)
  - 3 adult patient groups (N = 18)
  - 2 adolescent groups (N = 11)
- Outcomes/reactions from in-person and virtual (Zoom) focus groups similar
- Focus groups conducted in same manner as DPI focus groups
- Differences from DPIs to consider:
  - Emergency use product (vs. chronic, daily use)
  - Caregiver (not patient) may be user

EAIs: Brand and Generic Products

- Brand (RLD)

- Generic

User Interface differences noted and discussed by focus group participants:

- Size
- Brand – has carry case, no cap over needle end
- Generic – no carry case; has twist-off cap over needle end of EAI
- Different steps/number of steps

Manuscript submitted for publication

Study results and takeaways

- Patient and caregiver experience with and perceptions of generic drug products continue to expand and improve respectively.
- Patients and caregivers consistently appreciate the cost savings offered by generic DDCPs.
- There are lingering uncertainties and anticipatory anxiety about how differences between a generic DDCP and the brand-name DDCP (reference listed drug) will affect users' ability to user the generic successfully, especially in an emergency.
- Patients are frustrated by generic substitution of a DDCP when they are not informed that substitution may occur and why
- Additional plain language education for healthcare providers and patients about approval requirements for generic drugs (e.g., same quality) and that they have the same clinical effect and safety profile as the RLD may help address lingering questions

FY21 Grant Funding Opportunity

- **Goal:** Develop methods for evaluating the impact of differences in the design of the user interface of generic drug-device combination products compared to the RLD.

❖ Grantee

- University of Detroit, Mercy, School of Engineering
- Principal investigator: Megan Conrad, PhD
- Development of a Combination Product Taxonomy and Comparative Human Factors Testing Method for Drug-Device Combination Products Submitted in an ANDA

Grant Objectives/Aims

Aim 1: Information gathering

- Interviews with industry and academia
- Literature review
- Methodology search
- Investigation of design attributes (taxonomy development)

Aim 2: Develop a visual taxonomy

- Generate a content library for DDCPs
- Develop visual classification system
- Develop database of known potential use errors

Aim 3: Optimize

- Comparative analyses and comparative use human factors methodologies
- Conduct case study with noninferiority assessment

Interview results with nine industry experts

- Positive feedback:
  - Appreciate specific expectations outlined in guidance for comparative analyses and consider the process systematic and defined.
- Challenges:
  - Frustrated by different objectives described compared to the FDA guidance for human factors validations studies
  - Process for calculating sample size made complex by inability to obtain RLD data
  - Lack of methodology for computing and categorizing errors
  - Failure to address severity of errors
  - Confusion calculating acceptable error rates

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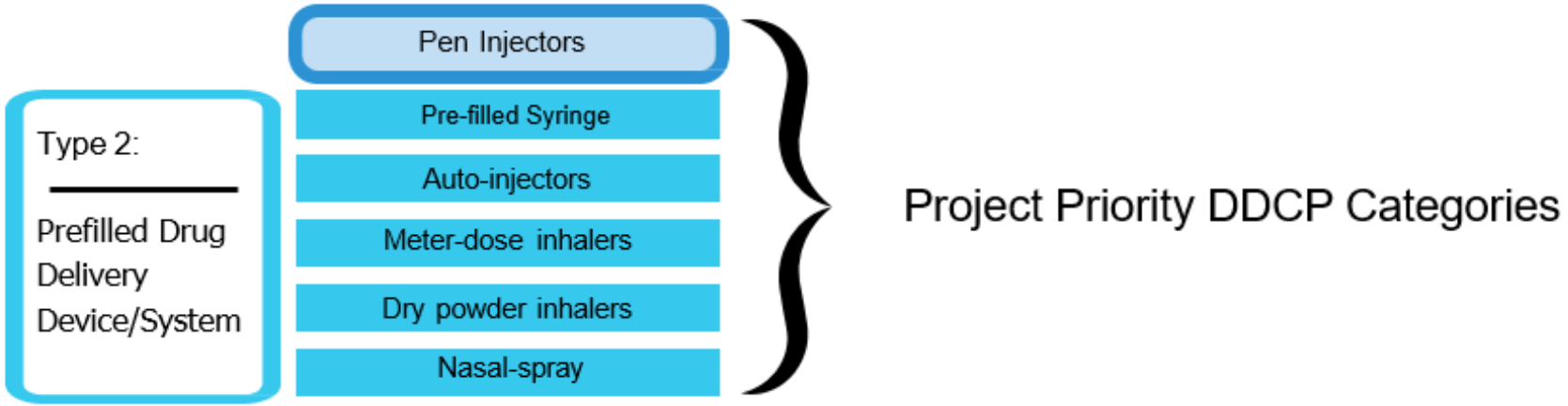
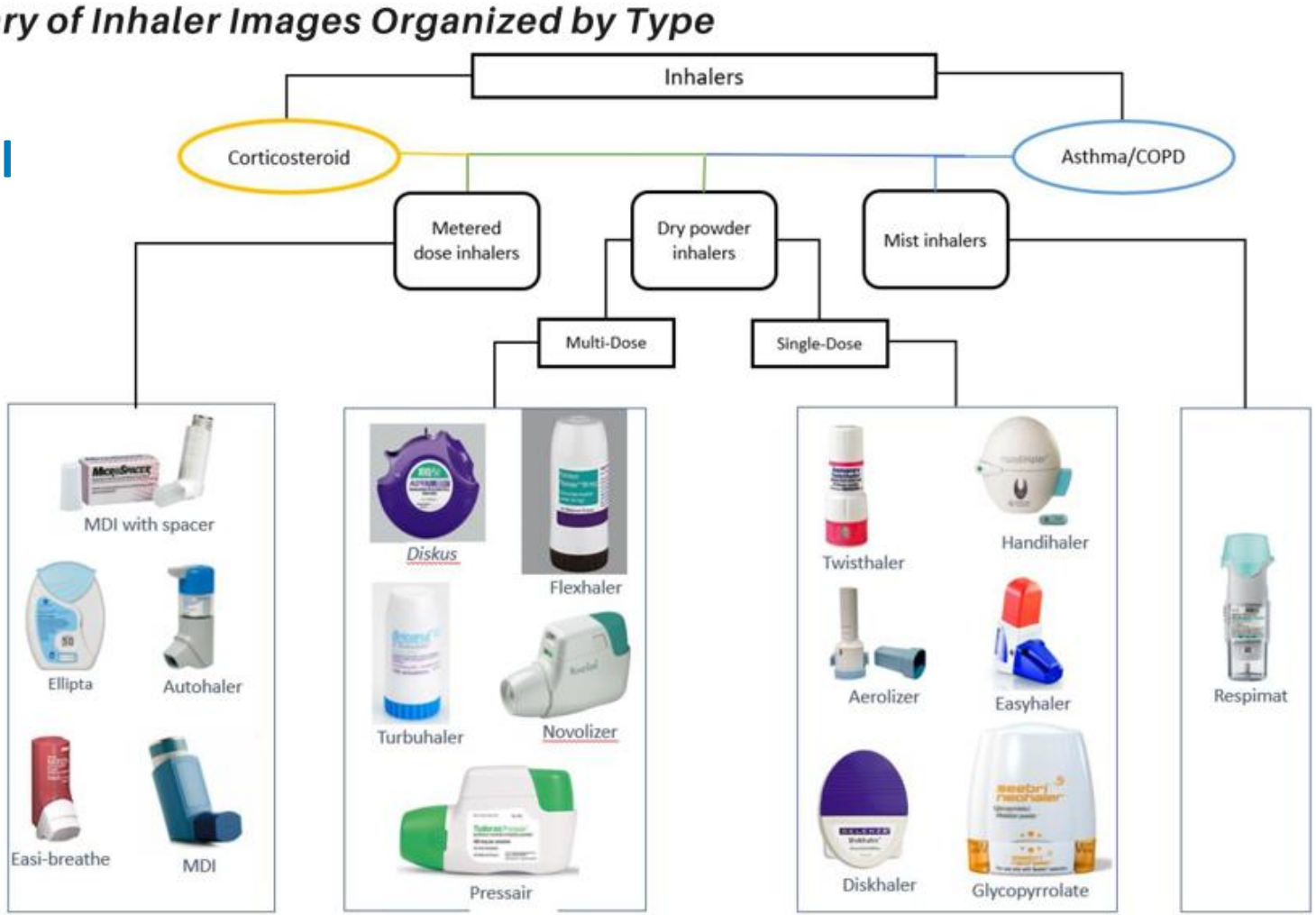
Aim 1: Classification of Medical Device and Label User Interface (UI) Design Attributes

- For different device types, identify points of user interaction
- Combination Products defined in 21 CFR 3.2(e):

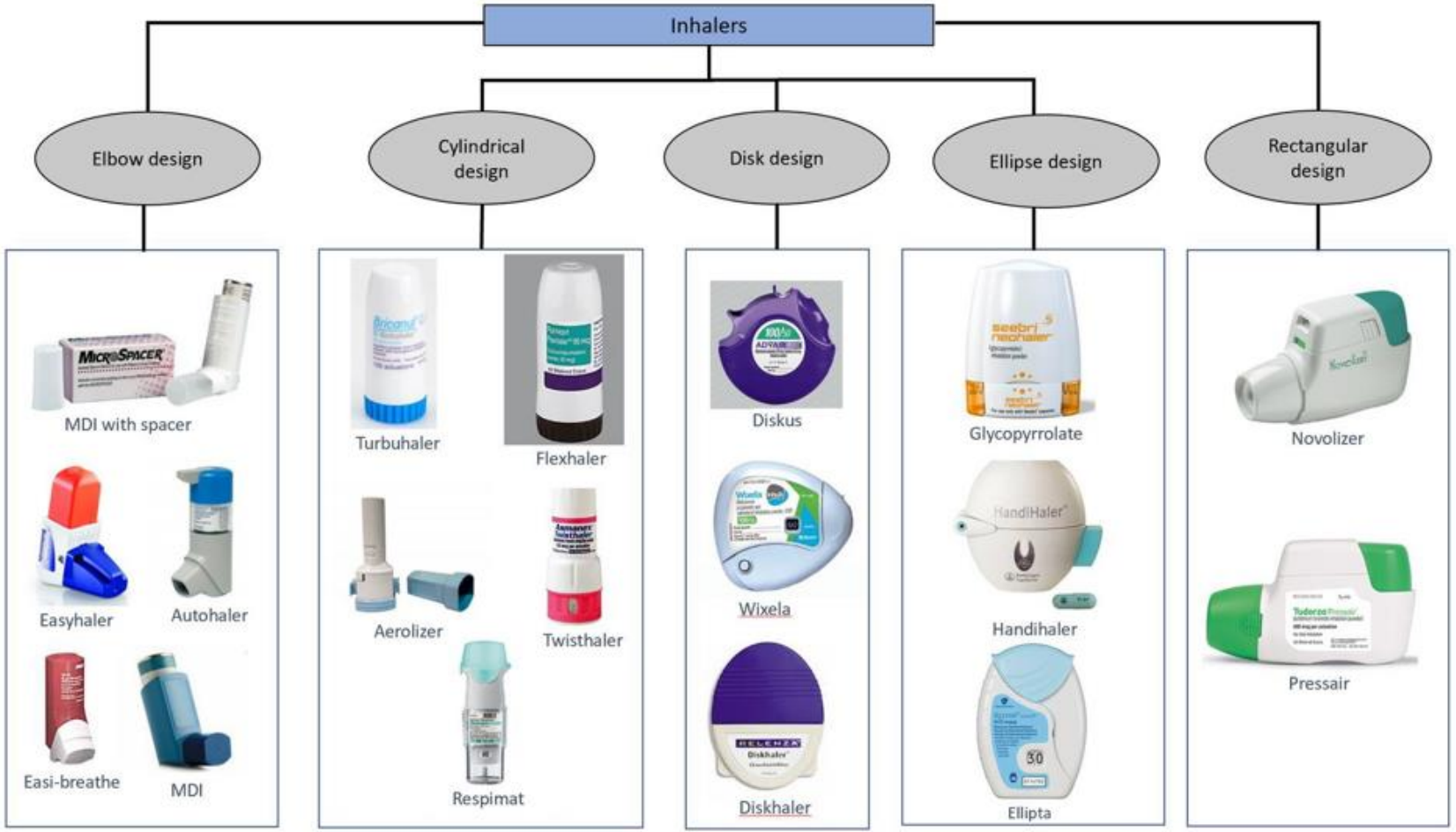


Develop Visual Classification System

based on design attributes in relation to potential harm associated with use error



Library of Inhaler Images Organized by Design

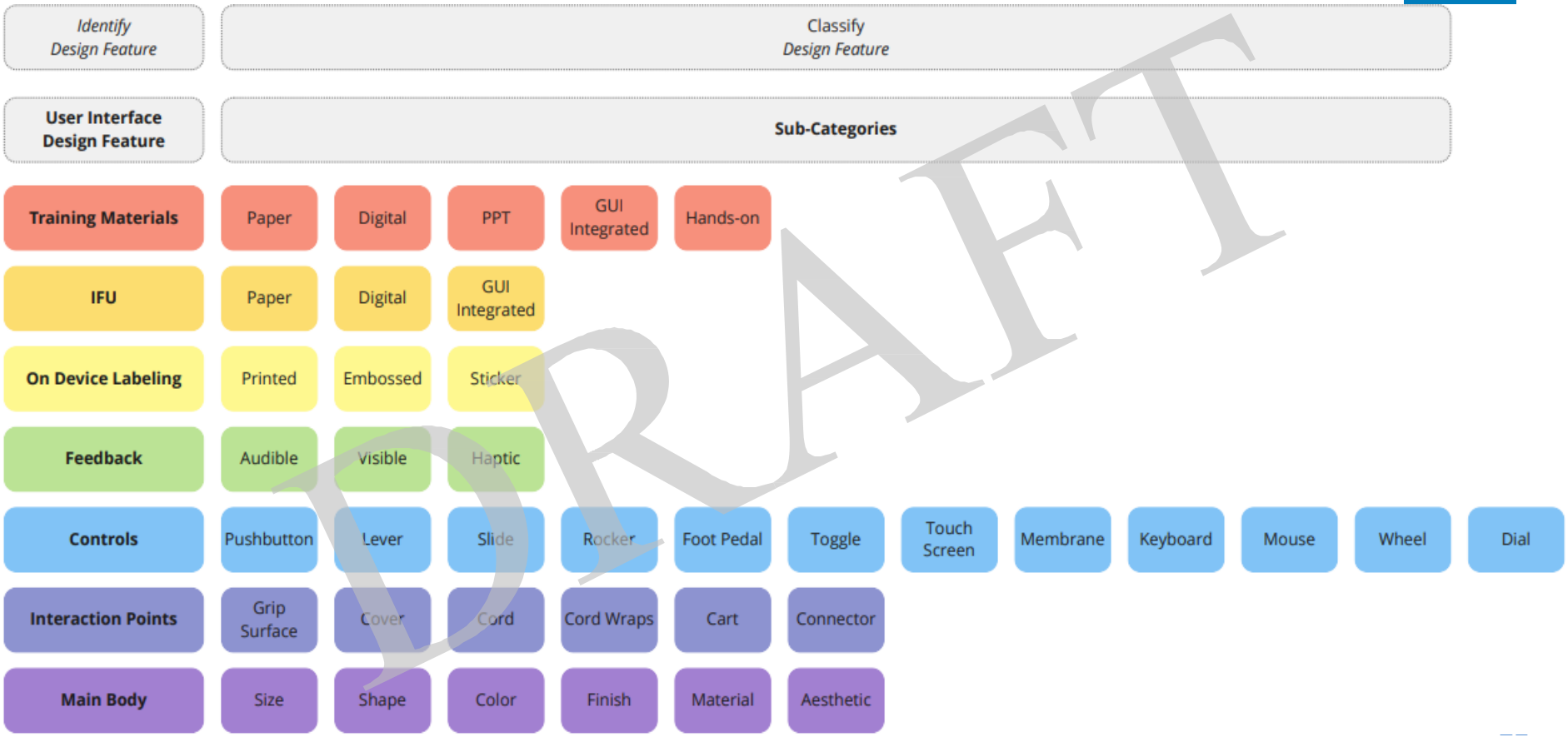


Aim 2: Develop visual taxonomy

- **Purpose of Activities:**
  - Develop Visual Taxonomy Related to UI Design Differences & Use-Related Risk
  - Method of simplifying, structuring and standardizing the identification and classification of differences in design attributes on DDCP user interfaces
  - Guide the process of determining “minor” vs “other” design differences
- Visual taxonomy can be applied from different perspectives, for example:
  - To describe physical design differences
  - To describe use task differences

Linking Design Features to Risk…

Structuring the Taxonomy



Structuring the Taxonomy

Example of process by task

Instructions on using Design Feature Taxonomy

1. Use Taxonomy to identify & classify design

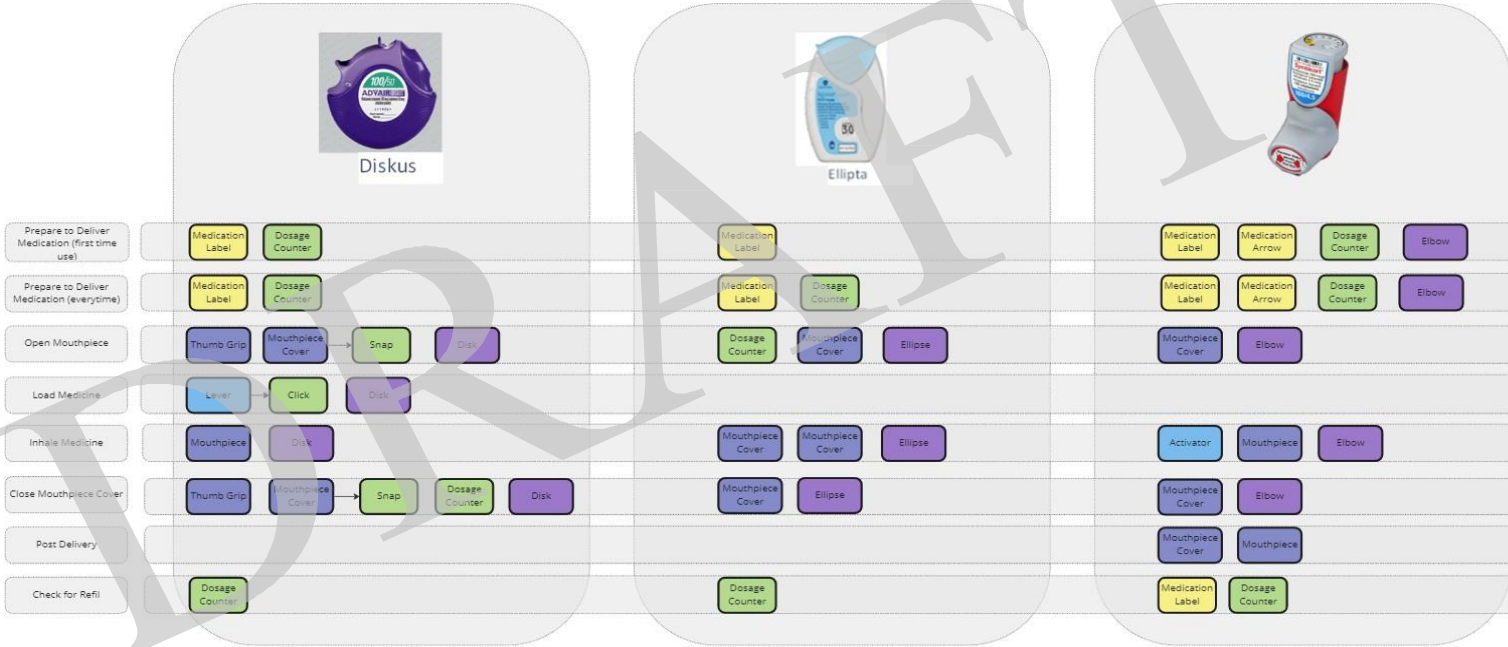
2. Use Task Analysis to relate design features to tasks

3. Conduct Risk Analysis [using TA]

4. Compare RLD to Generic based on taxonomy to determine design differences

Minor difference = change within a sub-category

Other difference = change in design feature identification (e.g., IFU is printed on device rather than paper handout)



2023 IDIQ Solicitation

- Comparative Use Human Factors Studies to Assess the Impact of Differences Between the User Interfaces of a Generic Drug-Device Combination Product and its Reference Listed Drug
- Primary objective:
  - Conduct multiple CUHF studies of complex drug-device combination products in relevant populations (e.g., patients and/or caregivers and/or health care providers) to assess the impact of “other” design differences between the user interfaces of an RLD and existing or potential generics referencing the RLD.

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Looking forward to your questions and the panel discussion