# Session 7:
# Drug-Device Combination Products


Karen B. Feibus, M.D.
Team Leader, Drug-Device Combination Products Team
Division of Therapeutic Performance-1, Office of Research and Standards
Office of Generic Drugs/CDER/FDA

# Session Objectives

## ❖ Review:

- How the Office of Generic Drugs compares device user interfaces (UIs) for proposed generic products and their reference listed drugs (RLDs)
- How the Office of Surveillance and Epidemiology uses comparative use human factors (CUHF) studies to evaluate the impact of “other than minor” differences between RLD and generic product UIs on user error rates when generic substitution occurs.

## ❖ Explore and discuss:

How additional research can enhance understanding of UI design difference and their impacts on successful drug delivery following generic drug-device combination product substitution:

- Improve and standardize approaches for identifying and categorizing UI differences as “minor” vs. “other”
- Inform development of a more predictable and consistent framework for UI difference assessment
- Address how lack of data impedes design and conduct of comparative use human factors studies
- Identify alternative study designs that can provide data to support same risk profile with UI differences between the RLD and a proposed generic product
- Address other challenges that impact development and assessment of generic drug-device combination products

# Session 7: Speakers/Panelists


| | | |
|---|---|---|
|  | Betsy Ballard, M.D.<br>Medical Officer/Physician<br>Drug-Device Combination Products Team, Office of Research and Standards, Office of Generic Drugs, CDER, FDA | Pre-ANDA Evaluation of Drug Delivery Device Constituents |
|  | Capt. Irene Chan, Ph.D.<br>Office of Medication Error Prevention and Risk Management, Office of Surveillance and Epidemiology<br>CDER, FDA | Comparative Use Human Factors Studies for ANDA Products |
|  | Melissa Lemke, Ph.D.<br>Biomedical Engineer<br>Regulatory Medical Device Human Factors Engineer<br>Founder, Human Ability Designs | URRA and Root Cause Analysis: The Secret Ingredients for Effective Comparative Use Human Factors Studies |

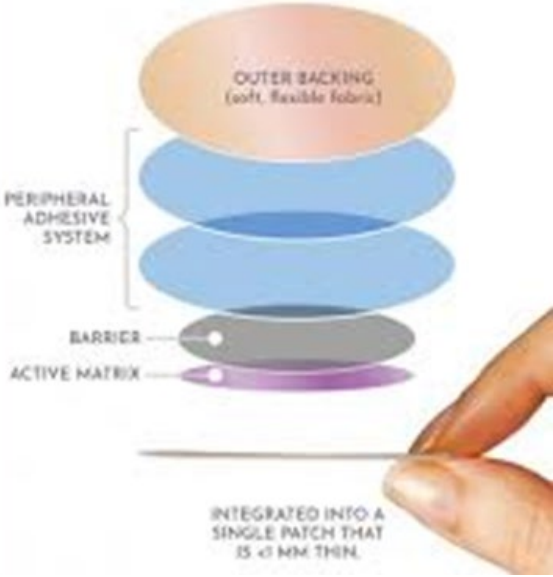
# Our Speakers/Panelists (2)

| | | |
|---|---|---|
|  | Mary Beth Privitera, M. Design, PhD<br>Principal, Human Factors & Research, HS Design<br>Director, Medical Device Innovation and Entrepreneurship Program, University of Cincinnati | Building a Taxonomy for Consistent Determination of Design Differences in Combination Products |
|  | Hailey Fehrenbach, MS<br>Industrial and Human Factors Engineer<br>Battelle Memorial Institute | Opportunities to Leverage Device Functional Assessment for Classifying and Evaluating User Interface Differences |
|  | Tracy Von Briesen, RN, MS<br>Director, Clinical Development<br>Fresenius Kabi | Insufficient Published Literature Related to the Usability of Device Constituent Parts |

# Our Additional Panelists

Chirag Walawalkar, B. Eng.
Associate Director,
Combination Products & Device Research and Development
Teva Pharmaceuticals

Yaping Zhu, PhD
Executive Director,
Device Development & Inhalation Development
Sandoz, Inc., a Novartis Division




FDA U.S. FOOD & DRUG ADMINISTRATION

U.S. FOOD & DRUG ADMINISTRATION

# Pre-ANDA Evaluation of Drug Delivery Device Constituents

Betsy Ballard, MD
Office of Research and Standards
Office of Generic Drugs, CDER

May 10, 2022

# Generic Drug Product Substitutability

In relation to the reference listed drug (RLD), generic products are expected to be:

- **Pharmaceutically Equivalent**

  The same active ingredient, dosage form, strength, route of administration and meet the same standards (strength, quality, purity, and identity)

- **Bioequivalent**

  No significant difference in the rate and extent of absorption of the active ingredient at the site of action

- **Therapeutically Equivalent**

  Approved drug products that are pharmaceutical equivalents for which bioequivalence has been demonstrated, and that can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling.

# What is a Combination Product?

21 CFR 3.2 (e) defines a combination product as composed of any combination of:

- a drug and a device;
- a biological product and a device;
- a drug and a biological product; or
- a drug, device, and a biological product.

# Classifications of Combination Products

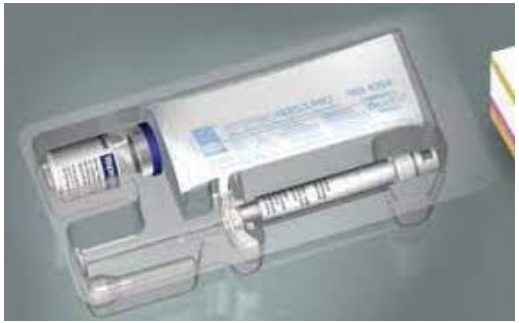
Per the Office of Combination Products:

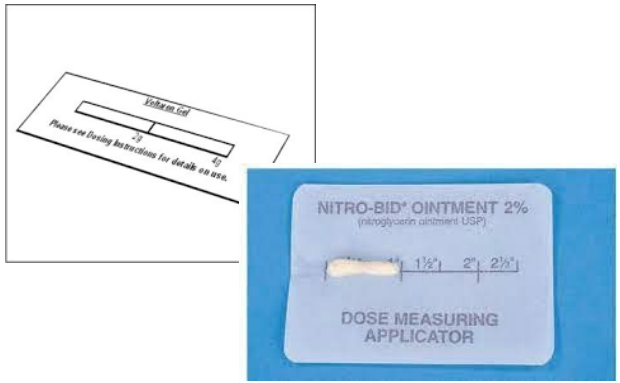
- There are 9 types of combination products
- Types 3, 5, 6, 8, and 9 relate only to biologic-containing combination products
- **Types 1, 2, 4, and 7** relate to drug-containing combination products

www.fda.gov/media/80384/download
www.fda.gov/combination-products/about-combination-products/combination-product-definition-combination-product-types

# Type 1 Combination Products:

## Convenience Kit or Co-Packaged Product





# Type 2 Combination Products:

## Pre-filled Drug Delivery Device/Systems

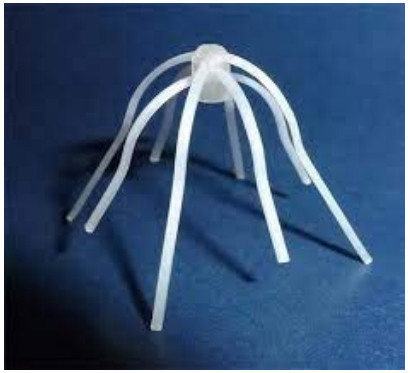
- Sole purpose of the device is to deliver drug



# Type 4 Combination Products:

## Device Coated/Impregnated/Otherwise combined with drug

– Device has additional function (and delivers drug)



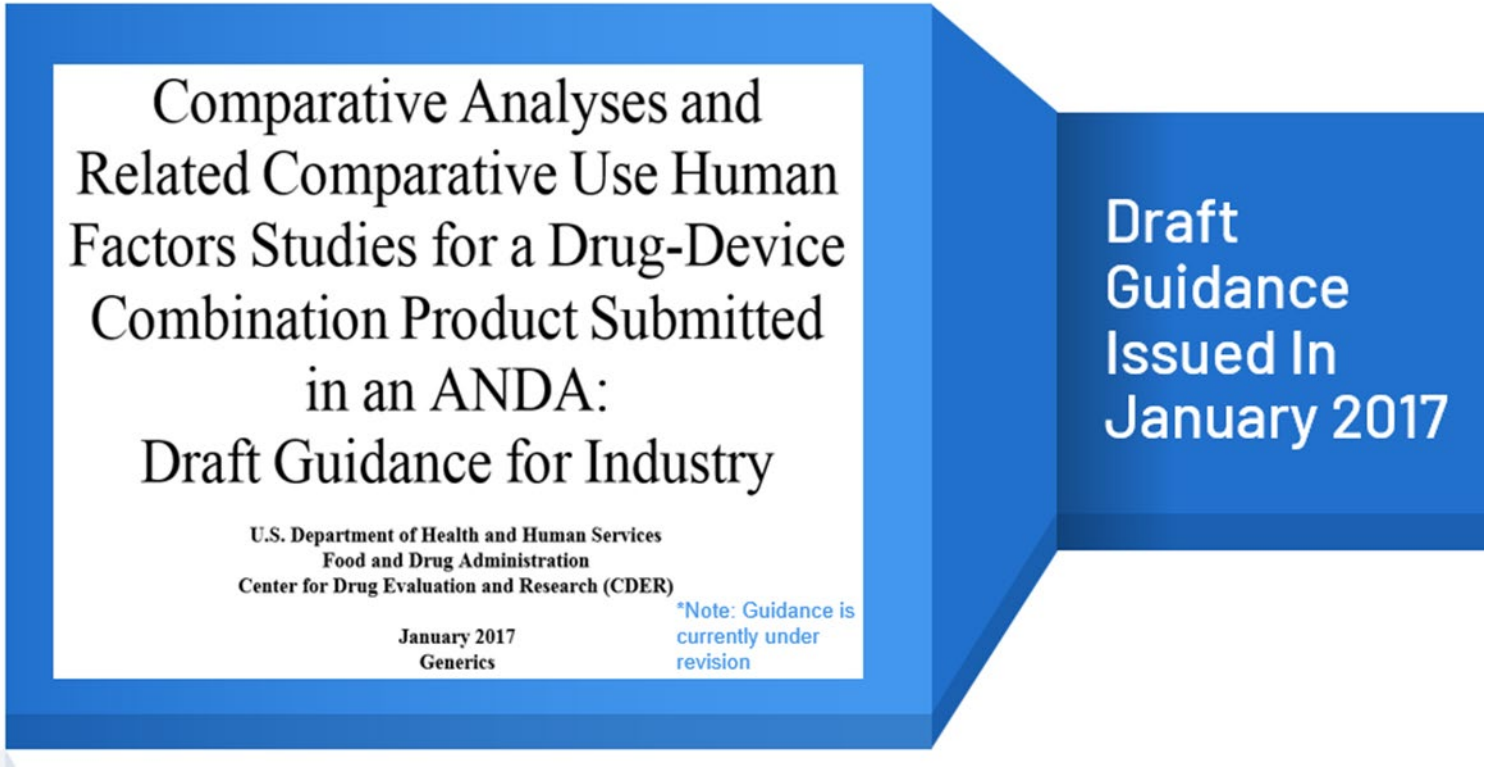
# Type 7 Combination Product

## Separate Products Requiring Cross-Labeling

– Example:  light-activated drugs that are not co-packaged but labeled for use with a specific device



# Comparative Analyses Guidance




https://www.fda.gov/media/102349/download

# Key Points From Draft Guidance

- The design does not have to be identical to the RLD
- Differences in the design of the user interface should be adequately analyzed, scientifically justified, and not otherwise preclude approval under an ANDA
- Design differences in the design of the user interface should be minimized in early phases of drug development
- Certain labeling differences may be allowed (case by case basis)
- End-users of generic combination products must be able to use the generic combination product safely when it is substituted for the RLD and without additional training

# Key Points From Draft Guidance

- Baseline assessment for any identified differences occurs during comparative analyses
- Will determine whether additional information and/or data is warranted
  - May include Comparative Use Human Factors Studies
  - Not intended to demonstrate the safety or effectiveness of the proposed generic combination product

# General Principles of Comparative Analyses

Considerations include, but are not limited to:

- Performance characteristics
  - Takes into consideration the performance of the device constituent and its interaction and impact on drug delivery
  - Not the focus of the Comparative Analyses.
- User Interface
  - Focus of review and evaluation in a comparative analyses

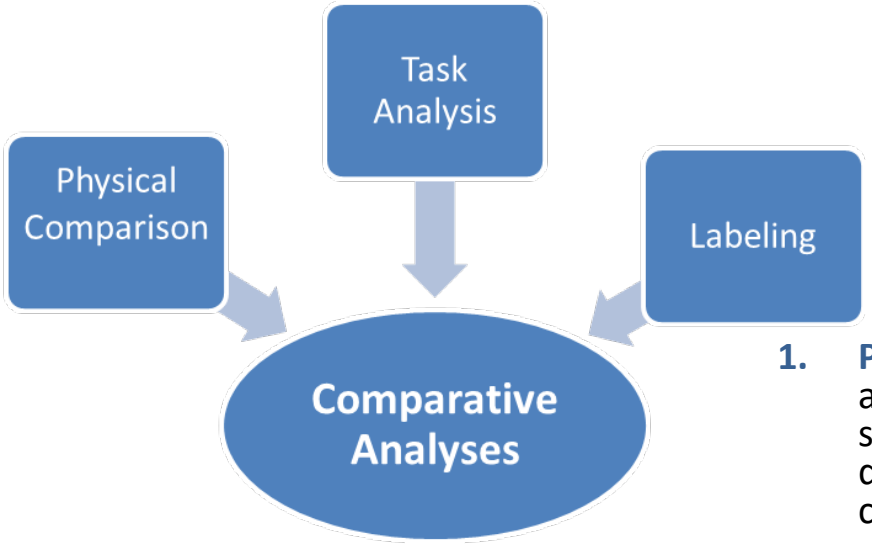
# Definitions

- **User Interface:** all components of a product with which a user interacts,
  - labeling and packaging,
  - the device delivery constituent part,
  - any associated controls and displays

- **External Critical Design Attributes:** Those features that directly affect how users perform a critical task that is necessary to use or administer the drug product

- **Critical Tasks:** Tasks 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 medical care

# Comparative Analyses (CA)




1. **Physical Comparison of Device Constituent Parts:** Visual, auditory, tactile examination of the physical features (size, shape, feedback) of the RLD, compared to those of the delivery device constituent part of the proposed generic combination product
2. **Comparative Task Analysis:** Comparative task analysis is assessed between the RLD and the proposed generic drug-device combination product
3. **Labeling Comparison:** 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

# CA: Outcomes of Comparisons

In the context of the *overall risk profile* of each comparison made between the proposed generic and RLD, user interfaces should be assigned one of the following outcomes:

- **No Difference**
- **Minor Difference**
  - A difference in the proposed generic user interface, in comparison to the RLD user interface, that does not affect an external critical design attribute
- **Other than Minor Difference**
  - A difference in the proposed generic user interface, as compared to the RLD user interface that ***may*** impact an external critical design attribute that involves administration of the product

# CA: Pre-ANDA Assessment Outcomes

- Complete vs. incomplete
- If incomplete, may involve one or more of the individual analyses.
- Common omissions and errors include (but are not limited to):
  - Missing comparative measurements or images
  - Omitted tasks
  - Omitted comparison outcomes (no, minor, or other difference) or justification of differences
  - Missing sections of the IFU
  - Text changes in labeling unrelated to change in manufacturer/distributor

# CA: Examples of Common Omissions

| Physical Comparison | Comparative Task Analysis | Labeling Comparison (IFU for Pre-ANDA) |
|---|---|---|
| No dimensions provided on comparative images | Use of the IFU comparison as a substitute for identifying the critical tasks | Images don't accurately depict the proposed product |
| Differences identified but not categorized as recommended in the Guidance | Not linking an identified physical difference to performance of a specific task | Certain sections are omitted such as any preparation and cleaning steps |
| Minor or other differences identified but not justified | URRA submitted instead of Comparative Task Analysis | Changes in text that may not be permissible and/or unrelated to a minor difference |

# URRA vs. Comparative Analyses

**Table 1. Example Row URRA for Formative Evaluation**

| Task | Potential use error(s) | Potential Hazard/Hazardous Situation | Potential harm | Severity of potential harm | Risk control measures | Critical task (Yes/No) |
|---|---|---|---|---|---|---|
| Remove cap | User twists cap while removing it | Clogged needle/no medication will flow. | Potential reduction of efficacy / worsening of symptoms. | Serious | Statements under "Remove cap" step in instructions stating:<br>• "Remove the cap by pulling it straight off," and<br>• "Do not twist the cap." | Yes |
| | | Clogged needle/no medication will flow. | Potential reduction of efficacy / worsening of symptoms. | Serious | | |
| | | Foreign body/injection of foreign body. | Infection (injection of needle shield fragment). | Serious | | |

| A threshold analysis should include the following human factors analyses: | | |
|---|---|---|
| 1 | **Labeling comparison** | Side-by-side, line-by-line comparison between the proposed product and the product it references that includes<br>• full prescribing information,<br>• instructions for use,<br>• container labels and carton labeling, and<br>• descriptions of the products |
| 2 | **Comparative task analysis** | A comparative task analysis of the proposed product and the product it references (comparator) |
| 3 | **Physical comparison of device UIs** | Examine, through a visual or tactile examination, the physical features of the product that it plans to reference and compare them to those of the proposed product |

# Key Takeaways

- A Complete CA includes:
  - A **physical comparison** of the proposed generic and RLD device user interfaces (including measurements).
  - A **comparative task analysis** that includes all tasks needed to correctly administer the drug (including prep steps and cleaning).
  - A **labeling comparison**. During pre-ANDA assessment, the focus is on the IFU. During ANDA review, all labeling components are evaluated.

- Pre-ANDA assessment of CA can provide feedback about:
  - Whether a proposed device may be appropriate for an ANDA submission.
  - Whether there may be "other than minor differences" between the user interfaces that may warrant submission of additional data to the ANDA to support that the differences won't alter the overall risk profile of the proposed generic product, as compared to the RLD.

- Generic product labeling should be the same as that of the RLD, although some differences related to manufacturer/distributor are permissible as described at 21 CFR 314.94(a)(8)(iv).

# Recommendations

1. Read and understand the draft guidance for industry, *Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA*.

2. Throughout drug-device combination product development,
   - Consider user interface and critical tasks of the RLD product
   - Evaluate risks associated with each identified difference between the proposed generic and RLD user interfaces
   - Perform iterative comparative analyses and seek to minimize differences from the RLD.

https://www.fda.gov/media/102349/download

# Recommendations (cont.)

3. Consider user interface differences in terms of whether they impact an external critical design attribute that involves product administration.

4. If your device design is final, then consider whether additional data (beyond the CA) are needed to support/justify any remaining user interface differences (e.g., a Comparative Use Human Factors study or other in vivo or in vitro study).

5. Talk early and often with FDA through:
   - controlled correspondences
   - pre-ANDA meeting requests for complex products.

# Acknowledgements


- Lisa Bercu, JD
- Karen Feibus, MD
- Markham Luke, MD, PhD
- Kimberly Witzmann, MD


FDA
U.S. FOOD & DRUG
ADMINISTRATION

FDA U.S. FOOD & DRUG ADMINISTRATION

# Comparative-Use Human Factors Studies for ANDA Products

**FY22 Generic Drug Science and Research Initiatives Public Workshop**

**Irene Z. Chan, PharmD, BCPS**

**Deputy Director**

**Office of Medication Error Prevention and Risk Management (OMEPRM)**

Center for Drug Evaluation and Research (CDER)

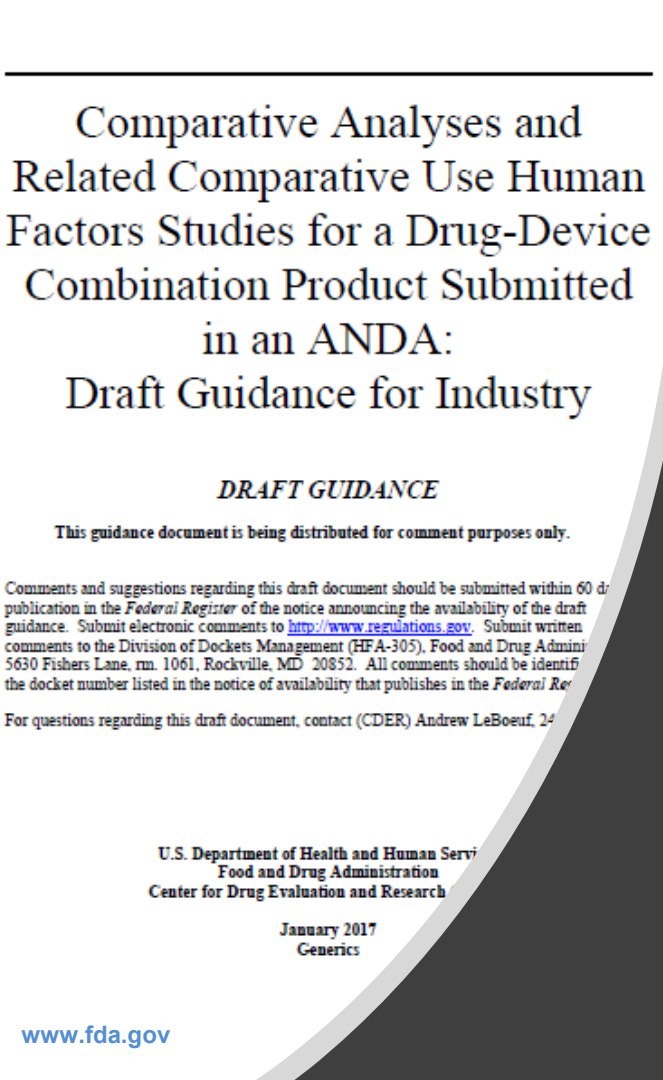
# Disclaimer

For work prepared by US government employees representing their agencies, there is no copyright and these work products can be reproduced freely.

Reference to any marketed products is for illustrative purposes only and does not constitute endorsement by the U.S. Government, the Department of Health and Human Services, or the Food and Drug Administration.

# Objectives

- Describe what the objective of a comparative-use human factors (CUHF) study is
- Review the steps involved in designing a CUHF study
- Present an example of a hypothetical CUHF study
- Review tips for submitting a CUHF protocol


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 d
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 Admini
5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identifi
the docket number listed in the notice of availability that publishes in the *Federal Re*

For questions regarding this draft document, contact (CDER) Andrew LeBoeuf, 24

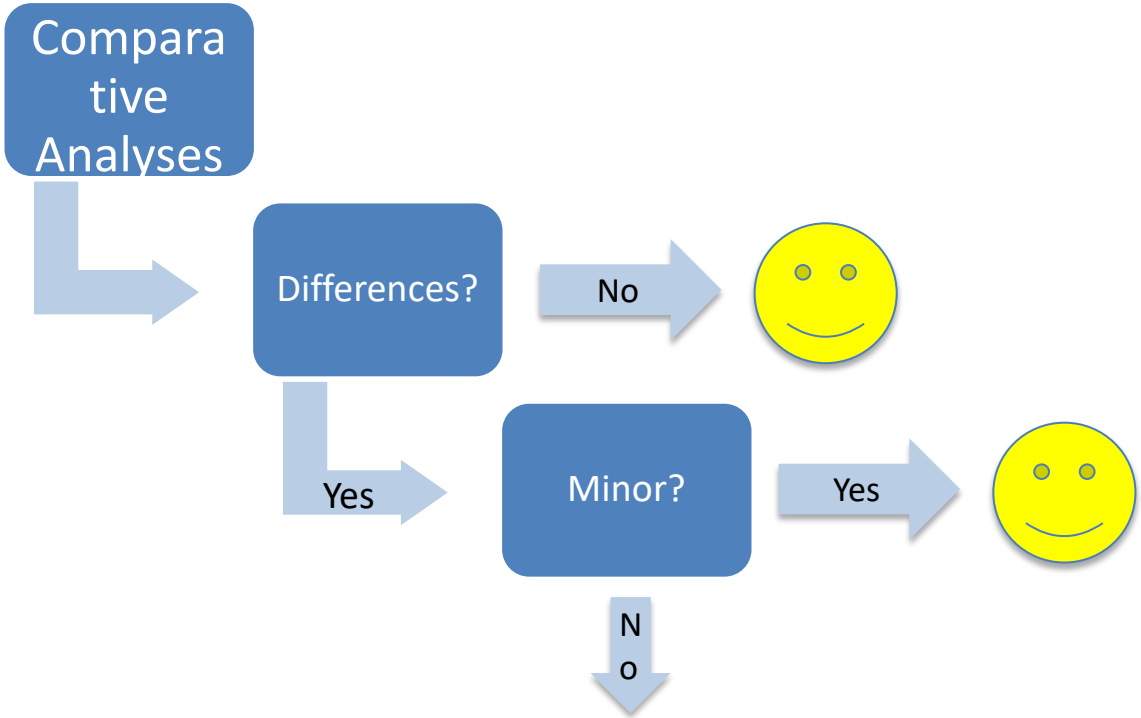
**U.S. Department of Health and Human Servi**
**Food and Drug Administration**
**Center for Drug Evaluation and Research**

**January 2017**
**Generics**

# Are you familiar with this draft guidance?

Focuses on the analysis of the proposed user interface for the generic drug-device combination product (generic combination product) when compared to the user interface for the reference listed drug (RLD)

# Process Overview




Further discussions with agency – additional information and/or data, such as data from a comparative use human factors (CUHF) study, may be warranted

# Remember…

- ANDAs rely on FDA's finding of safety and effectiveness for their RLD
- Requires demonstration of "sameness" of a number of characteristics + additional information to permit reliance
- Generic combination products classified as therapeutically equivalent to the RLD can be expected to produce the same clinical effect and safety profile as the RLD under the conditions specified in the labeling

# So what does that mean?

- You're not establishing new safety and efficacy for the proposed generic
- Generic products are essentially confirming "sameness" to the reference listed drug (RLD)

**Comparative approach**

# CUHF Study

- **Objective is to demonstrate that differences would not preclude approval of the proposed product in an ANDA**
- **Generally simulated use study**
- **Noninferiority (NI) study designs are generally appropriate**
  - **Goal: show patient experience using generic combination product will be no worse than that with RLD with some allowance for random variation**

# So what steps do I need to take?

1. Identify who your users will be
    - FDA's focus is on whether substitution can occur with a full expectation that the generic product will produce the same clinical effect and safety profile
        - Include current end-users of the RLD
            - Consider if your analyses indicate that specific subpopulations should be the focus of a study
                - Consider whether a difference in design may impact critical task performance for patients diagnosed with certain indications only

# So what steps do I need to take?

2. Identify your delta, *d*
   - Con[illegible]hat prov[illegible] rates for the
   - You[illegible]r than $ER_R$ + *d*, [illegible] $ER_R$
     - *d*[illegible]owance for random variance with $ER_R$ that is expected
     - *d* should take into account the risk that any difference in outcome will pose to the patient (i.e., what is the clinical consequence associated with a critical task failure)
   - Be prepared to justify how you derived *d*

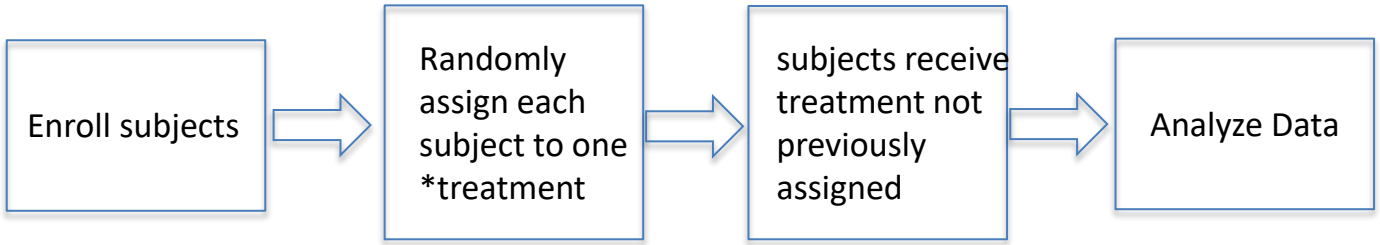
**This is a very important step that forms the basis for creating a statistical test that will allow you to demonstrate that differences would not preclude approval of the proposed product in an ANDA**

# So what steps do I need to take?

3. Decide on paired design or parallel design to NI study
    - Paired design will generally be applicable and more efficient with respect to resources
        - Subjects should be randomly assigned to the sequence of use, such as AB or BA, to control for order effects

# Paired Study Design

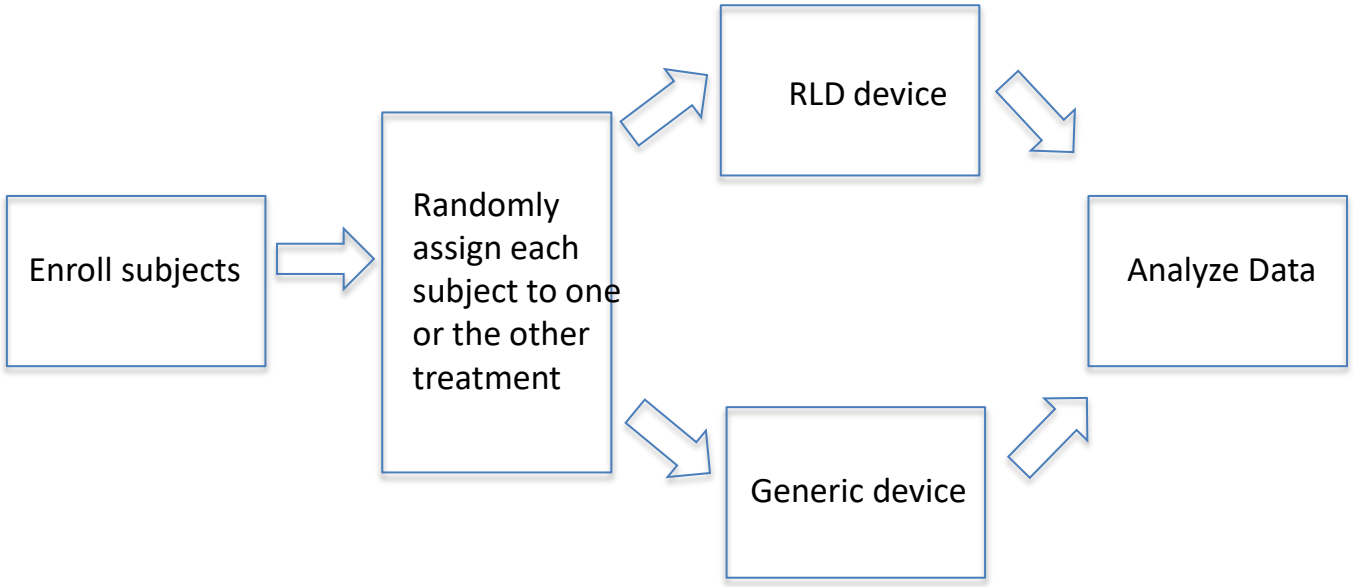
Each subject is his or her own control




- The sample size is often smaller than that required for a parallel design
- Analysis must consider correlation within subjects (success rates in the two treatments not independent)

*treatment is defined as a condition being applied to experimental units (subjects) to elicit outcomes which can be compared. Therapies are often treatments in clinical trials. Here, use of combination product will be a treatment.

# Parallel Study Design




- Usually requires larger sample size than paired design
- Statistical tests with this design are often more straightforward than for the paired design

# So what steps do I need to take?

4. Calculate your study sample size considering assumed

   - Keep i rates are succes
   - Typica robability (α) will be set at 5%
     - Type 1 error: Reject a true null hypothesis (false positive)
     - Type II error: non-rejection of a false null hypothesis (false negative)

**Consult your statisticians!**

# So what steps do I need to take?

5. Submit your study protocol to the FDA and get feedback before initiating a CUHF study
   – Controlled correspondence or pre-ANDA meeting

# So what steps do I need to take?

6. Observe error rates and success rates for the critical task(s) during the study
    - When observing the study, you can assign a binary value of 0 or 1 to users for each critical task performed where 1 is assigned to successful task completion and 0 is assigned to task failures

# So what steps do I need to take?

7. Perform your statistical hypothesis test, comparing the upper bound of appropriate level confidence interval for the difference in event rates to *d*

$$H^0: ER^T - ER^R \geq d$$
$$H^A: ER^T - ER^R < d$$

Rejecting the null hypothesis ($H^0$) in favor of the alternative hypothesis ($H^A$) supports the claim of NI as defined by *d*

# So what steps do I need to take?

8. Alternatively, if study design is based on success rate, then perform your statistical hypothesis test based on:

$$H^0: SU_R - SU_T \geq d$$
$$H^A: SU_R - SU_T < d$$

Rejecting the null hypothesis ($H^0$) in favor of the alternative hypothesis ($H^A$) supports the claim of NI as defined by *d*

# Let's walk through a hypothetical example…

- RLD is an emergency use product marketed as prefilled syringe with a cap that snaps off
- Generic proposes a prefilled syringe that has a cap that threads off (requires user to twist)
- Threshold analyses outcome: One other than minor difference exists (for this example, we assume that cap removal is a critical task)
  - Consider that intended users may encounter more difficulty with twisting off the cap, and in a substitution scenario, are likely to try to snap the cap off as they are accustomed to with the RLD

# Example

- Endpoint?
  - Focus on task of cap removal
    - Patients NOT successfully removing the cap
- Each subject operates both devices (paired)
- Randomize order within subject (T, R or R, T)
- Other details as appropriate, mask devices, etc….
- Test
  - Null hypothesis:

    %Failing goal (Test) - %Failing goal (RLD) ≥ 10%
  - Alt hypothesis:

    % Failing goal (Test) - % Failing goal (RLD) < 10%

# Example continued…

- Sample size of approximately 50, assuming:
  - 90% of subjects able to correctly remove cap (based on information in the literature)
  - 80% power
  - Type I error probability of no more than 5%
  - Within subject correlation: 0.90

# Example Analysis

- Example results:

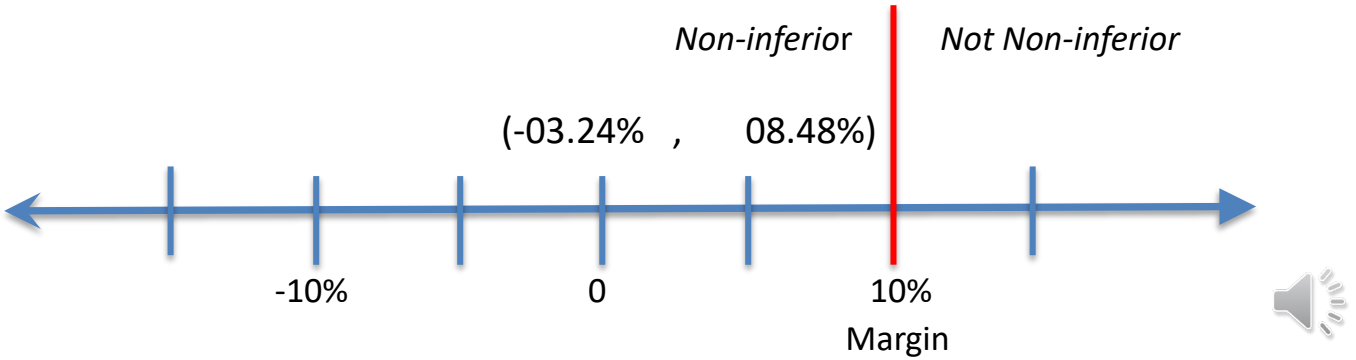
6%-4%=2%

90% CI: (-03.24, 08.48)

| | | | RLD | |
|---|---|---|---|---|
| | | S | U | |
| Test product | S | 47 | 0 | 47 |
| | U | 1 | 2 | **3** |
| | | 48 | **2** | 50 |

S: successful attempts
U: unsuccessful attempts

The upper bound of the 90% CI is less than the 10% margin,
ruling out a difference of greater than 10% with 95% confidence.
(this is like doing a one-sided test at 0.05 level)



# Example Alternative…

- Endpoint?
  - Focus on task of cap removal
    - Patients successfully remove the cap
- Each subject operates both devices (paired study design)
- Randomize order within subject (T, R or R, T)
- Other details as appropriate (e.g., mask products)
- Statistical Test (assuming *d* set at 10%)
  - Null hypothesis:

    %achieving goal (RLD) - %achieving goal (Test) ≥ 10%
  - Alt hypothesis:

    %achieving goal (RLD) - %achieving goal (Test) < 10%

# Example Analysis

- Example results:

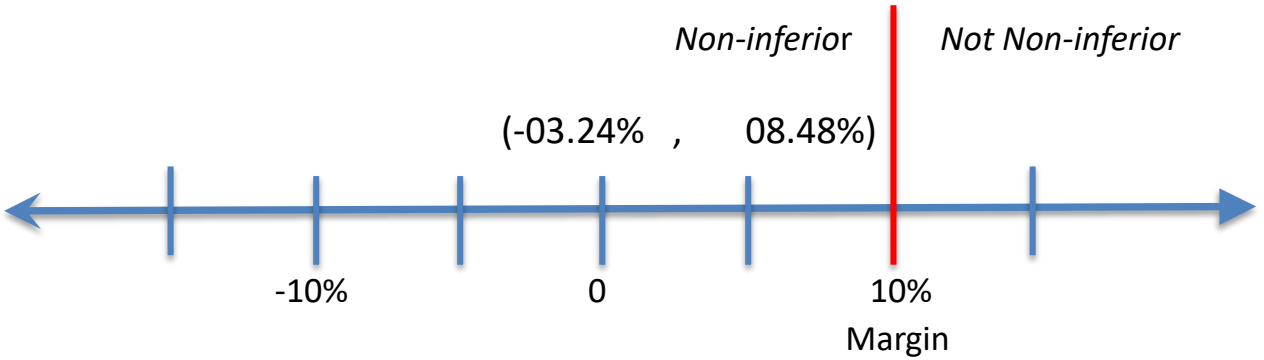
96%-94%=2%

90% CI: (-03.24, 08.48)

| | | | RLD | |
|---|---|---|---|---|
| | | S | U | |
| Test product | S | 47 | 0 | **47** |
| | U | 1 | 2 | 3 |
| | | **48** | 2 | 50 |

S: successful attempts
U: unsuccessful attempts

The upper bound of the 90% CI is less than the 10% margin,
ruling out a difference of greater than 10% with 95% confidence.
(this is like doing a one-sided test at 0.05 level)



# Tips for Submitting Your CUHF Protocol

- Clearly identify user interface design differences
  - Include your threshold analyses (comparative analyses)
- Ensure you recruit appropriate expertise to inform your statistical analysis plan
  - Explain how you derived delta, *d*
- Provide 5 samples of your product
- Refer to additional information in draft guidance: *Contents of a Complete Submission for Threshold Analyses and Human Factors Submissions to Drug and Biologic Applications*
- Wait on agency advice before proceeding with your study


FDA
U.S. FOOD & DRUG
ADMINISTRATION

Human Ability Designs

# URRA and Root Cause Analysis:
## The Secret Ingredients for Effective Comparative Use Human Factors Studies

Melissa Lemke
Founder & Principal Human Factors Engineering Consultant
May 10, 2022

# About Human Ability Designs

Melissa Lemke

FOUNDER

**Human Ability Designs**

https://humanabilitydesigns.com/

- We provide human factors engineering **consulting and training** for designers and developers of medical and drug delivery devices.
- Human Factors Reviews, Mastering HFE™ Training, SME on call
- Led by Melissa Lemke, a biomedical engineer with 18 years in the industry, AAMI HF instructor, Instructor at UW-Milwaukee
  - Lay caregiver turned professional HFE
  - 100% success designing and implementing rigorous HF programs to get safe & effective products onto the market for hundreds of clients

# Our Core Team

**Dr. Megan O. Conrad**

Dr. Megan Conrad at University of Detroit Mercy leads the grant efforts as the PI. Students Julie Ann Piechocki and Karlee Lambert also support the research activities.

**Melissa R. Lemke, MS**

Human Ability Designs provides regulatory human factors consulting and outcomes based training to product designers and developers of medical devices and combination products.

**Dr. Mary Beth Privitera**

HS Design is a full service user centered design firm specializing in Medical and Digital Health product and user interface design.

**Dr. Molly F. Story**

Human Spectrum Design provides consulting on human factors for medical devices and combination products, particularly to satisfy FDA requirements, minimize use-related risk, and provide a superior user experience.

# Our FDA Funded Human Factors Research Goal

**Develop an Improved Comparative Use Human Factors (CUHF) Method**

To identify and analyze user interface (UI) design differences that may impact substitutability of an RLD and proposed generic drug device combination product (DDCP) for clearance through the FDA ANDA pathway.

**Considering the Needs of Key Stakeholders**

End Users: Lay Users and Healthcare Professionals
FDA Reviewers
Pharmaceutical Industry (and Consultants)
Academic Researchers

# FDA Draft Guidance[1]

**Comparative Analyses and Related C**
**Use Human Factors Studies… (2**

- Draft guidance lays posit
  rigorous comparative a
  proposed generic for a
  ANDA pathway
- Threshold Analysis + CUHF
  thorough but lacks important
  related risk

**Key public comments on the draft guidance:**

- Concerns with FDA focus on use error rates rather than potential harms or root causes of use errors
- Industry desires a qualitative analysis similar to FDA (and other international standards) HF validation study

same clinical

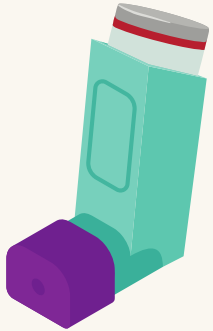
ituted for RLD
d/or without

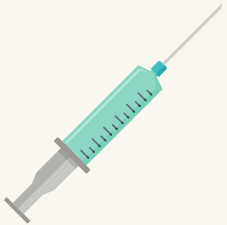
1. Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA: Draft Guidance for Industry: https://www.fda.gov/media/102349/download

# Our Team's R&D Process (2021-2024)

To Develop Use Related Risk Analysis (URRA) Based CUHF Method

- Aim 1: Develop body of knowledge of key stakeholder perspectives of existing strategies
- Aim 2: Develop visual taxonomy to systematically analyze UI design attributes and identify minor and other design differences
- Aim 3: Develop improved CUHF method that relates to UI design differences that have the potential for introducing use errors on critical tasks that could result in harm or compromised medical care





# Early Survey Results – Aim 1

Aim 1: Develop body of knowledge of key stakeholder perspectives of existing strategies

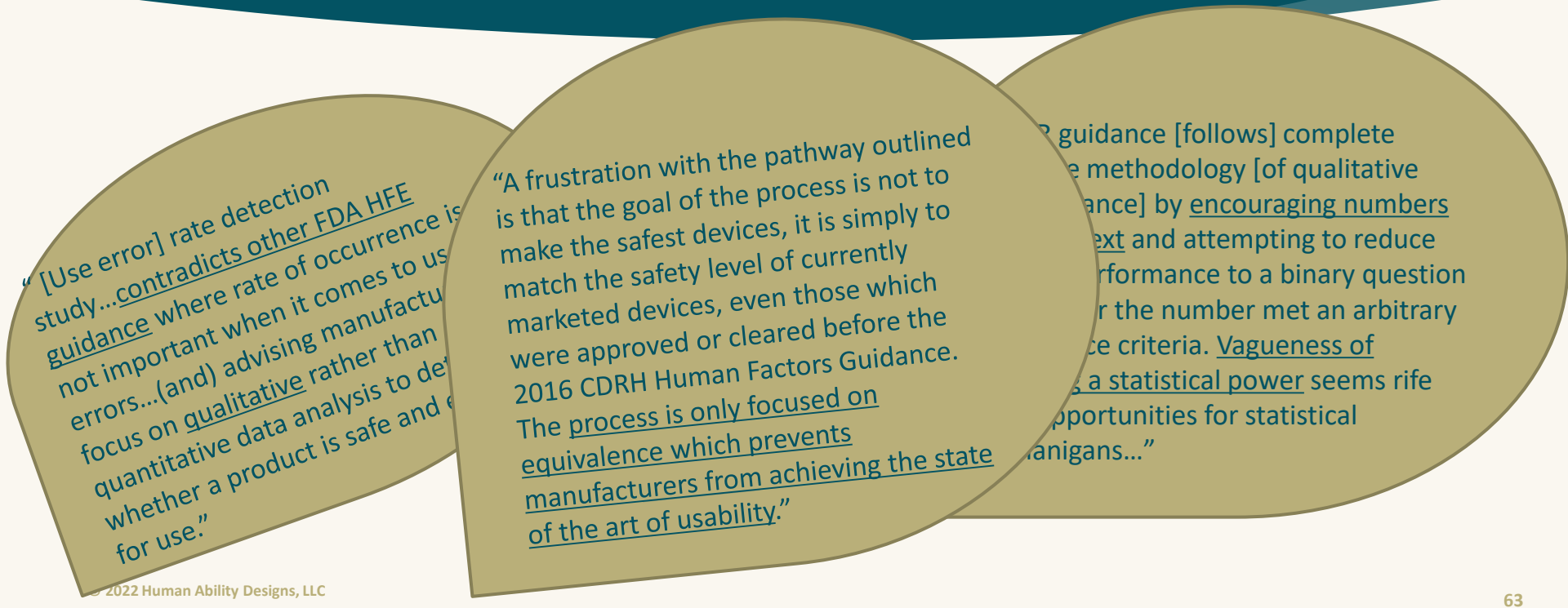
**Our early survey research (n=19) indicates:**

- Threshold analysis is straightforward, clear and easy
- Need clarification on what CUHF method should prove and if it replaces HF validation study
- Need specific method to identify minor versus other design differences related to use related risk and potential harm

**Survey respondents are:**

- HF practitioners from industry and consulting firms, Manager and Director level HF professionals
- Experienced with threshold analysis (3) and CUHF method (3)
- Experienced with conducting 1-6+ analyses
  - Pre-filled syringes
  - Auto-injectors, multidose pens
  - On-body injectors

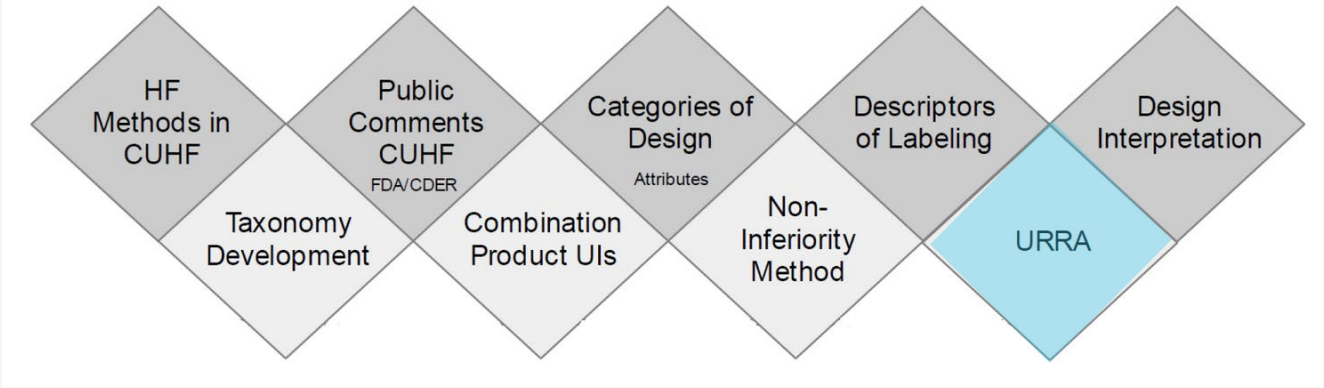
# Early Survey Results Support Our Team's Approach



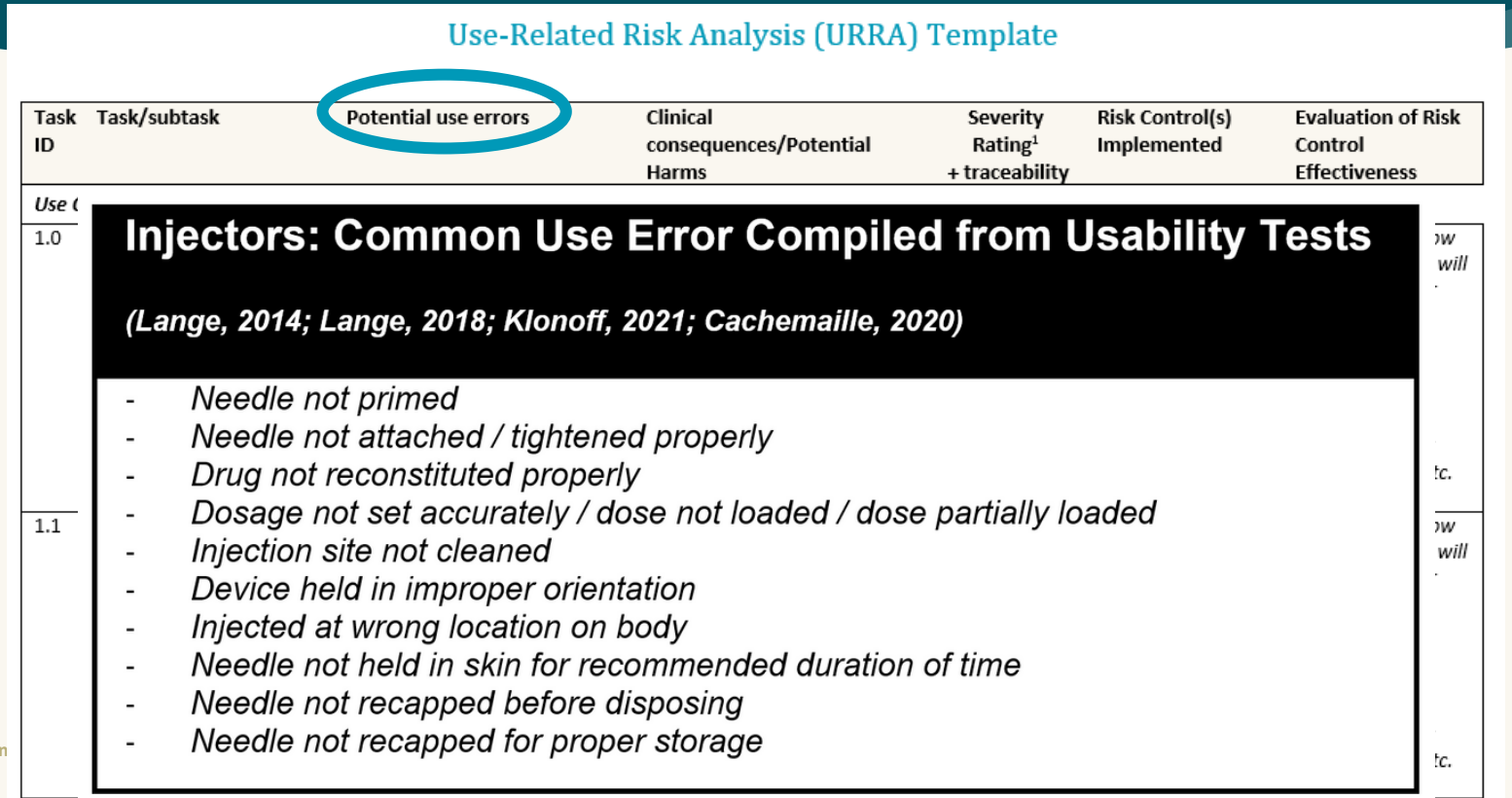
# Literature Review – Aim 1

Development of Use Related Risk Analysis Based Comparative Use Human Factors Method

- Aim 1: Develop body of knowledge of key stakeholder perspectives of existing strategies



# Use-Related Risk Analysis (URRA)



Use-Related Risk Analysis (URRA) Template

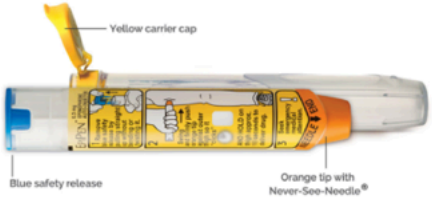
| Task ID | Task/subtask | Potential use errors | Clinical consequences/Potential Harms | Severity Rating[1] + traceability | Risk Control(s) Implemented | Evaluation of Risk Control Effectiveness |
|---|---|---|---|---|---|---|
| *Use C* | | | | | | |
| 1.0 | | | | | | |
| 1.1 | | | | | | |

**Injectors: Common Use Error Compiled from Usability Tests**

***(Lange, 2014; Lange, 2018; Klonoff, 2021; Cachemaille, 2020)***

- *Needle not primed*
- *Needle not attached / tightened properly*
- *Drug not reconstituted properly*
- *Dosage not set accurately / dose not loaded / dose partially loaded*
- *Injection site not cleaned*
- *Device held in improper orientation*
- *Injected at wrong location on body*
- *Needle not held in skin for recommended duration of time*
- *Needle not recapped before disposing*
- *Needle not recapped for proper storage*

# Use-Related Risk Analysis (URRA) Example




Epinephrine (EpiPen) – auto-injector

Use Indication: EpiPen® and EpiPen Jr® Auto-Injectors are for the emergency treatment of life-threatening allergic reactions (anaphylaxis) caused by allergens, exercise, or unknown triggers; and for people who are at increased risk for these reactions. EpiPen® and EpiPen Jr® are intended for immediate administration as emergency supportive therapy only. Seek immediate emergency medical help right away.

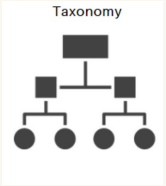
| Task ID | Task/subtask | Potential use errors (including known use problems) | Clinical consequences/ Potential Harms | Severity Rating[1] | Risk Control(s) Implemented |
|---|---|---|---|---|---|
| 1.0 | *Remove the auto-injector from the clear carrier tube. Flip open the yellow cap of the pen, then tip and slide the auto-injector out of the carrier tube.* | • *Not opening tube cap*<br>• *Not sliding device out of carrier tube.* | *No dose delivered* | *S-5* | • *Color coded tube cap*<br>• *Tube shape for grip*<br>• *Tub cap enables one hand use*<br>• *IFU explains task* |
| 1.1 | *Hold the auto-injector in your fist with the orange tip pointing downward. Blue to the sky, orange to the thigh.* | • *Holding device in incorrect orientation* | *Potential injection into thumb* | *S-5 patient*<br>*S-4 caregiver* | • *On device labeling: NEEDLE END*<br>• *Color coded safety release (blue) and needle end (orange)*<br>• *Labeling: On device label and IFU explain task* |
| 2.0 | *Ensure the blue safety release is not raised. If blue safety release Is raised, do not use the* | • *Using auto-injector when blue safety release is raised, causing the device to activate by accident.* | *No dose delivered* | *S-5* | • *Labeling: IFU explains task* |

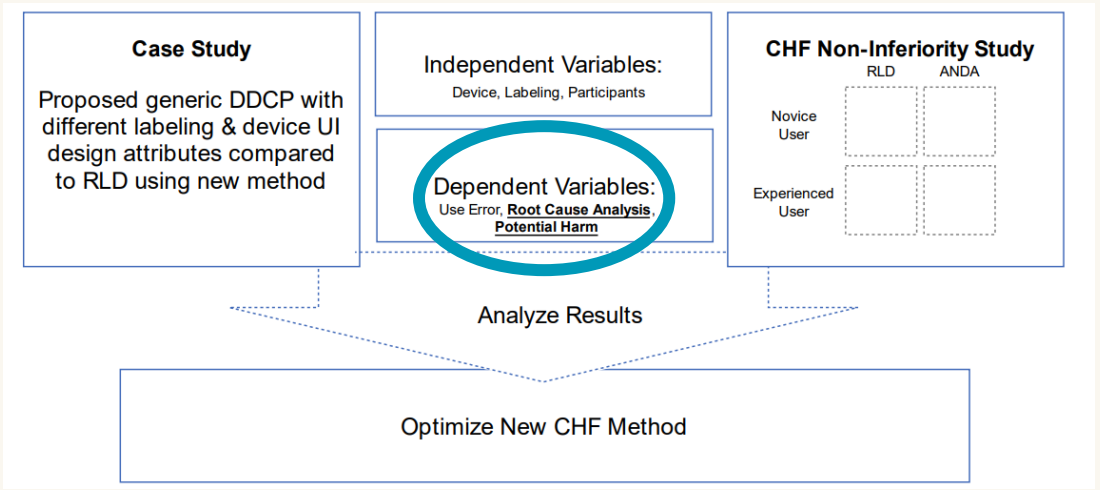
# Our Team's Process – Aim 3

To Develop Use Related Risk Analysis (URRA) Based CUHF Method

- Aim 3: Develop improved CUHF method that relates to UI design differences that have the potential for introducing use errors on critical tasks that could result in harm or compromised medical care

Use Related Risk Analysis (URRA) Based Threshold Analysis & Visual Taxonomy



# Root Cause Analysis Creates Meaningful HF Comparisons

| Context of use errors | Problematic Device Design Features | Problematic Labeling Design Features | Potential Design Improvements |
|---|---|---|---|
| Some use errors are not attributed to the combination product design or design differences | Could be with the RLD and/or proposed generic device design | Could be with the RLD and/or proposed generic labeling design | Root Cause Analysis provides meaning to use errors |
| Some use errors are not attributed to | Could be due to order effect during testing | Could be due to order effect during testing | Improvements are likely in new labeling due to iterative design |

# Key Takeaways

## Use Related Risk Analysis

- Key to improved Threshold Analysis and CUHF method
- Provides foundation for a complete human factors analysis
- Provides meaningful context to the currently required task analysis
- Provides details and linkage between use related tasks (performance and knowledge), potential use errors, potential harms, and user interface design features

## Root Cause Analysis

- Key to improved CUHF method and use error comparison
- Provides details needed for complete CUHF method
- Enhances the counting of use errors
- Provides details and prioritization of comparative use errors with conclusions from the usability data (performance of critical tasks and subjective interview data)

# Thank you!

**Human Ability Designs**

https://humanabilitydesigns.com/

melissa@humanabilitydesigns.com

Phone: 414.704.4809

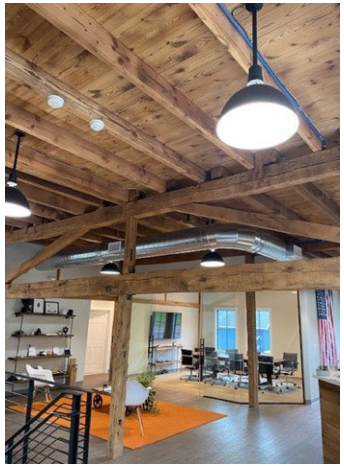
# Building a Taxonomy for Consistent Determination of Design Differences in Combination Products

Mary Beth Privitera, Mdes., PhD, FIDSA

2022 GDUFA Research Workshop
May 10, 2022

hs|d
A STERIPACK COMPANY

# Design & Development

- Award Winning Product Design & Development Firm
- 40 years experience in Medical, Life Science & Pharma
- Conducted research in over 50 leading medical institutions
- Located in Morristown, NJ

Consumer Health  Drug Delivery  Life Sciences  Medical & Surgical

bsi. ISO 13485 Medical Devices Quality Management

AAMI Advancing Safety in Medical Technology

hs|d
A STERIPACK COMPANY

# OUR TEAM

**Dr. Megan O. Conrad**

University of Detroit Mercy leads the grant efforts with Dr. Megan Conrad as the project PI. Students Julie Ann Piechocki and Karlee Lambert also support the research activities

**Melissa R. Lemke, MS**

Human Ability Designs provides regulatory human factors consulting and outcomes based training support to product designers and developers of medical devices and combination products.

**Dr. Mary Beth Privitera**

HS Design is a user centered design firm specializing in Medical and Digital Health product and user interface design.

**Dr. Molly F. Story**

Human Spectrum Design provides consulting on human factors for medical devices and combination products, particularly to satisfy FDA requirements, minimize use-related risk, and provide a superior user experience.

hs|d
A STERIPACK COMPANY

# Our FDA Funded Human Factors Research Goal

## Develop an Improved Comparative Use Human Factors (CUHF) Method

To identify and analyze user interface (UI) design differences that may impact substitutability of an RLD and proposed generic drug device combination product (DDCP) for clearance through the FDA ANDA pathway.

## Considering the Needs of Key Stakeholders

End Users: Lay Users and Healthcare Professionals
FDA Reviewers
Pharmaceutical Industry (and Consultants)
Academic Researchers

hs|d
A STERIPACK COMPANY

# Specific Aims:

- Aim 1: Develop body of knowledge of key stakeholder perspectives of existing strategies
- Aim 2: Develop visual taxonomy to systematically analyze UI design attributes and identify minor and other design differences
- Aim 3: Develop improved CUHF method that relates to UI design differences that have the potential for introducing use errors on critical tasks that could result in harm or compromised medical care

hs|d
A STERIPACK COMPANY

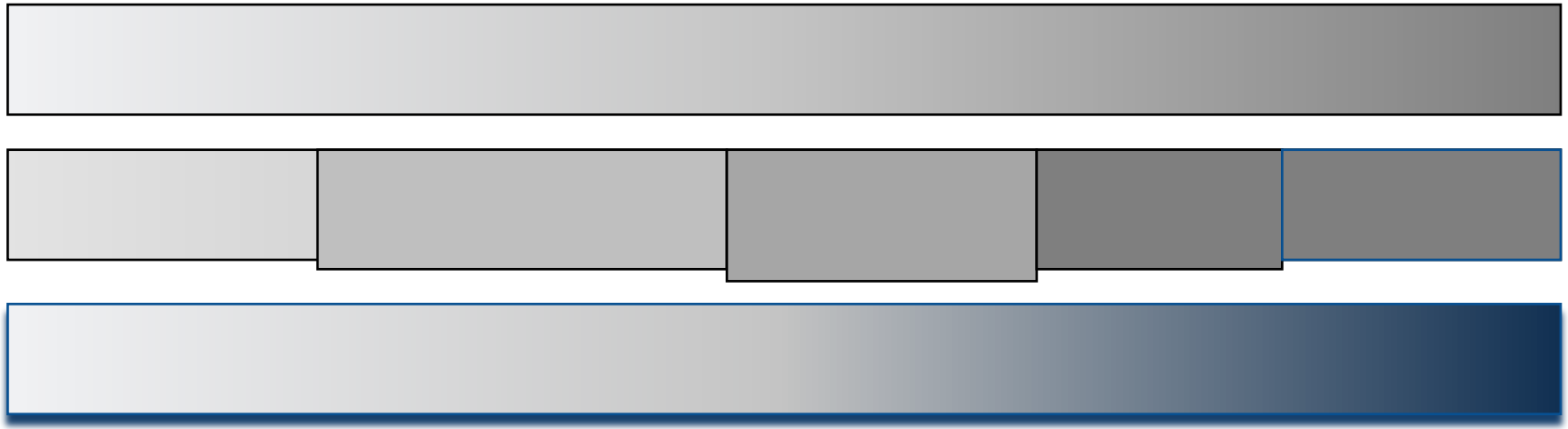
# FDA Draft Guidance[1]

- **Comparative Analyses and Related Comparative Use Human Factors Studies… (2017)**
  - After completing the threshold analyses, the following outcomes are possible:
    - No design differences
    - Difference in Design: Minor or Other

1. Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA: Draft Guidance for Industry: https://www.fda.gov/media/102349/download

hs|d
A STERIPACK COMPANY

# Is there a design difference?



Is it minor?  Is it “Other”? .....Does it matter?

And to whom? .....For what purposes?

hs|d
A STERIPACK COMPANY

# Distinguishing between designs depends on:

- Empirical evidence that users are able to distinguish between device variants (Schneider, 2019)

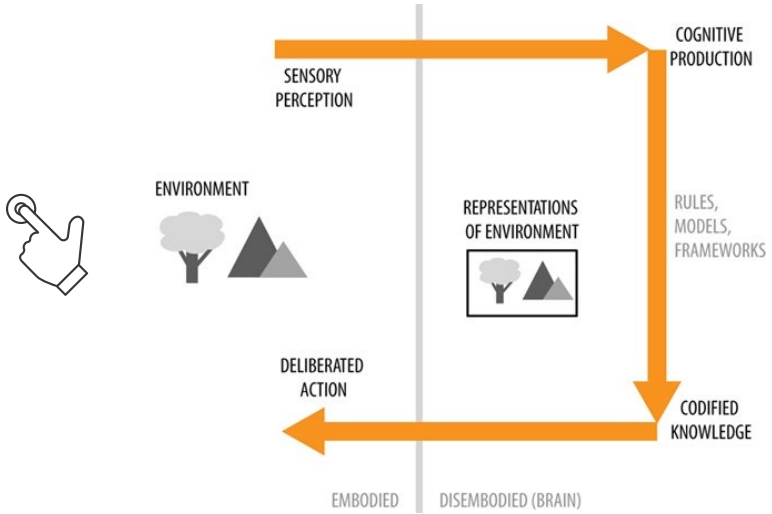
Context of Device Use

WHAT DRIVES HOW USER GROUPS DISTINGUISH DEVICE VARIANTS?

User group Characteristics

hs|d
A STERIPACK COMPANY

# Design Interpretation Matters

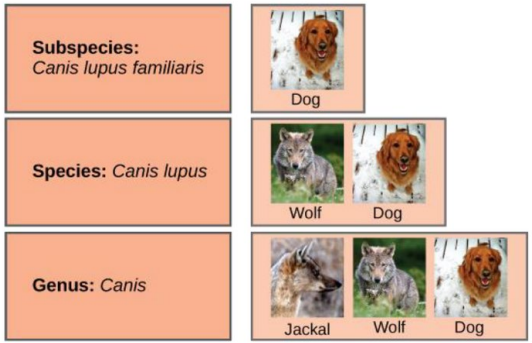


hs|d
A STERIPACK COMPANY

# Aim Two: Building a Taxonomy

- Taxonomy design - a method for organizing subject-specific concepts and creating a vocabulary for those concepts
- Provides order in organizing the attributes related to the concept/topic

Examples span biological research and education




Recognized in Human Factors

- Use of WHO's International Classification for Patient Safety (ICPS) as a human factors taxonomy to identify contributing factors for medical/surgical complications (Mitchell, 2018)

hs|d
A STERIPACK COMPANY

# What analysis techniques exist to determine design differences?

- Labeling Comparison
- Comparative Task Analysis
- Physical Comparison

Per FDA, CUHF must include:

L

**Labeling Comparison (generic <-> RLD)**

Side-by-side; line-by-line comparison

- Prescribing information
- IFU
- description of delivery device constituent parts

C

**Comparative Task Analysis**

Comparison Generic DDCP <--> RLD

- empasis on critical tasks

P

**Physical Comparison of Delivery Device**

Including visual and tactile examination of physical features

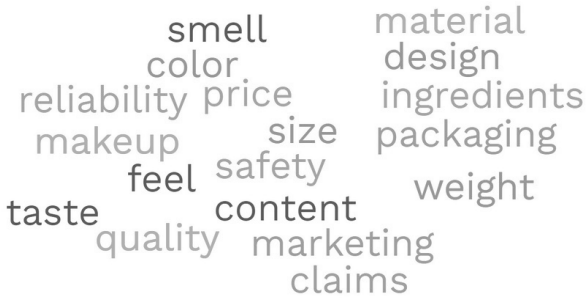
- size, shape, visual or tactile feedback

hs|d
A STERIPACK COMPANY

# What are User Interface attributes?

Key Takeaways from literature review:

- Scant literature focused solely on product design
- Emphasis placed on changing customer behavior and/or promoting brand influence




color, shape, size, texture, material

FDA Presentation (Witzmann & LeBoeuf, 2018)

External Critical Design Attributes "refers to those features that directly affect how users perform a critical task that is necessary in order to use or administer the drug product."

Product/labeling Attributes can be defined as:

Characteristics defining a service or product and influencing customer buying decisions

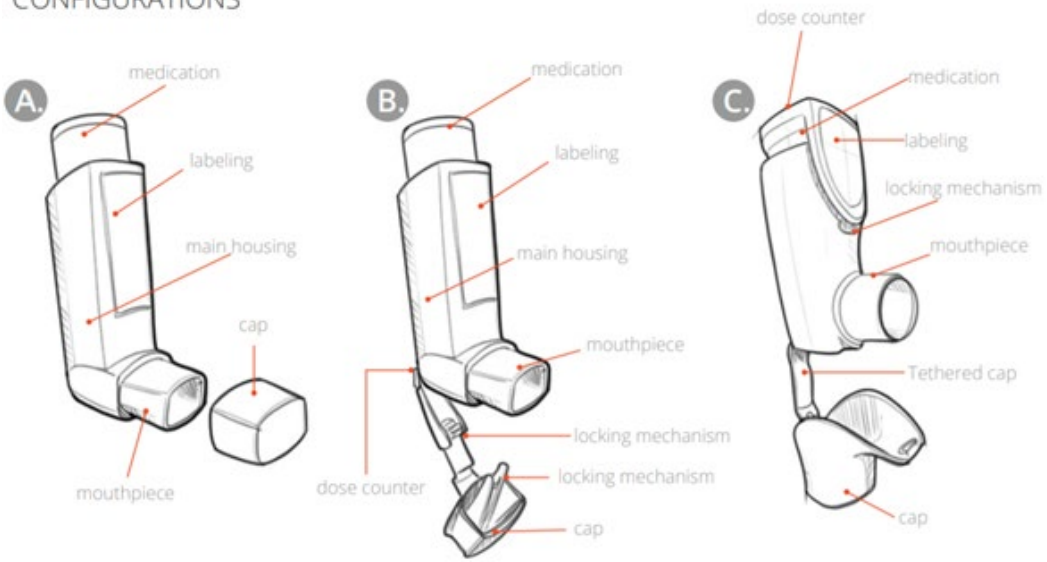
| Tangible (physical) | Intangible (perceptive/cognitive) |
|---|---|

# Examples

hs|d
A STERIPACK COMPANY

# ASTHMA INHALER TAXONOMY

## CONFIGURATIONS




## DESIGN POSIBILITIES

**Activation Button**

1. plastic part with tactile indents
2. side actuation/ button

**Mouthpiece**

1. round
2. oval
3. pillowed square
4. square
5. fluted

**Main Housing**

1. round
2. trapezoidal
3. pillowed square
4. square

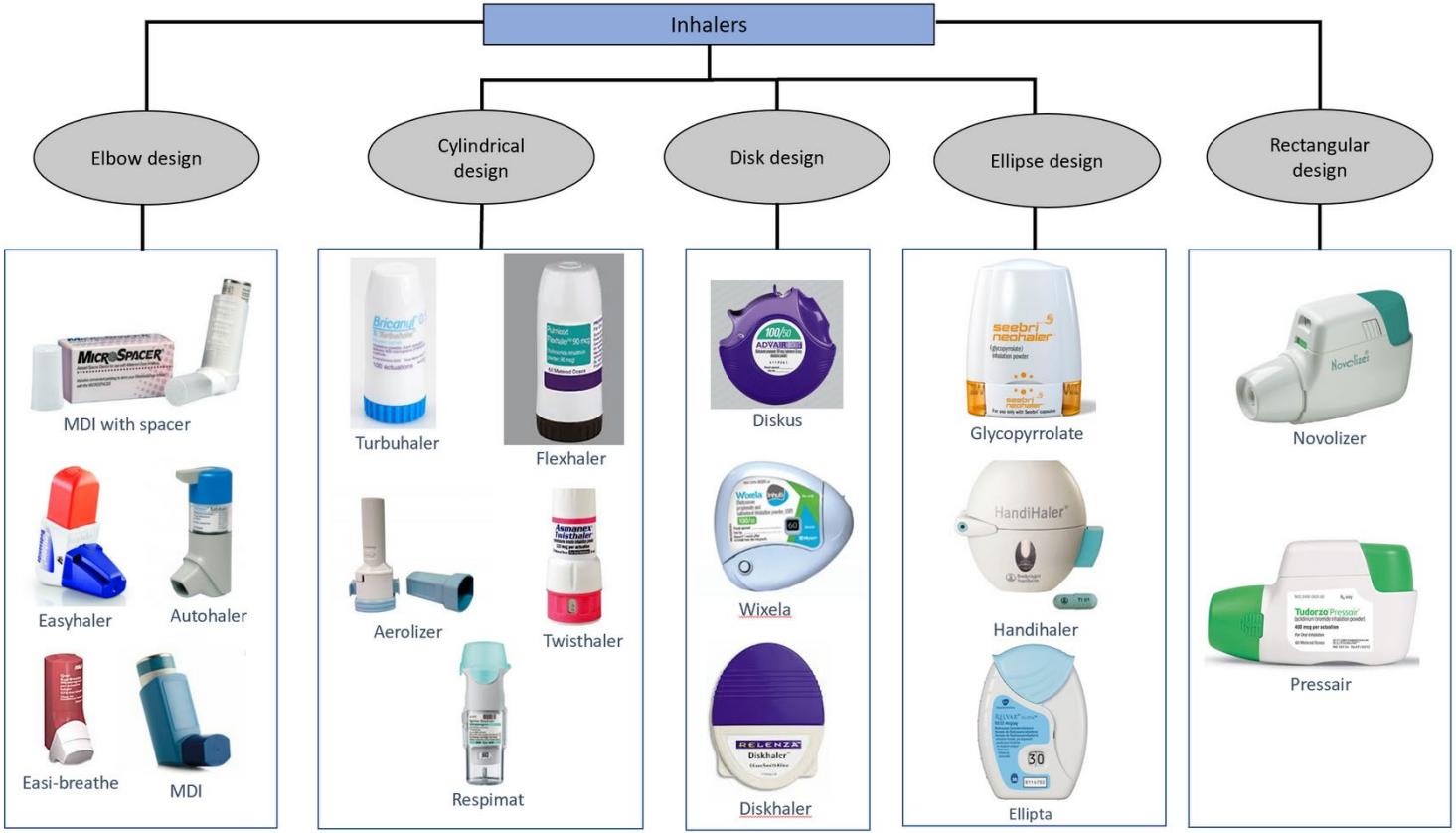
**Locking Mech.**

1. on cap
2. on main body
3. on medication cartridge
4. separate part

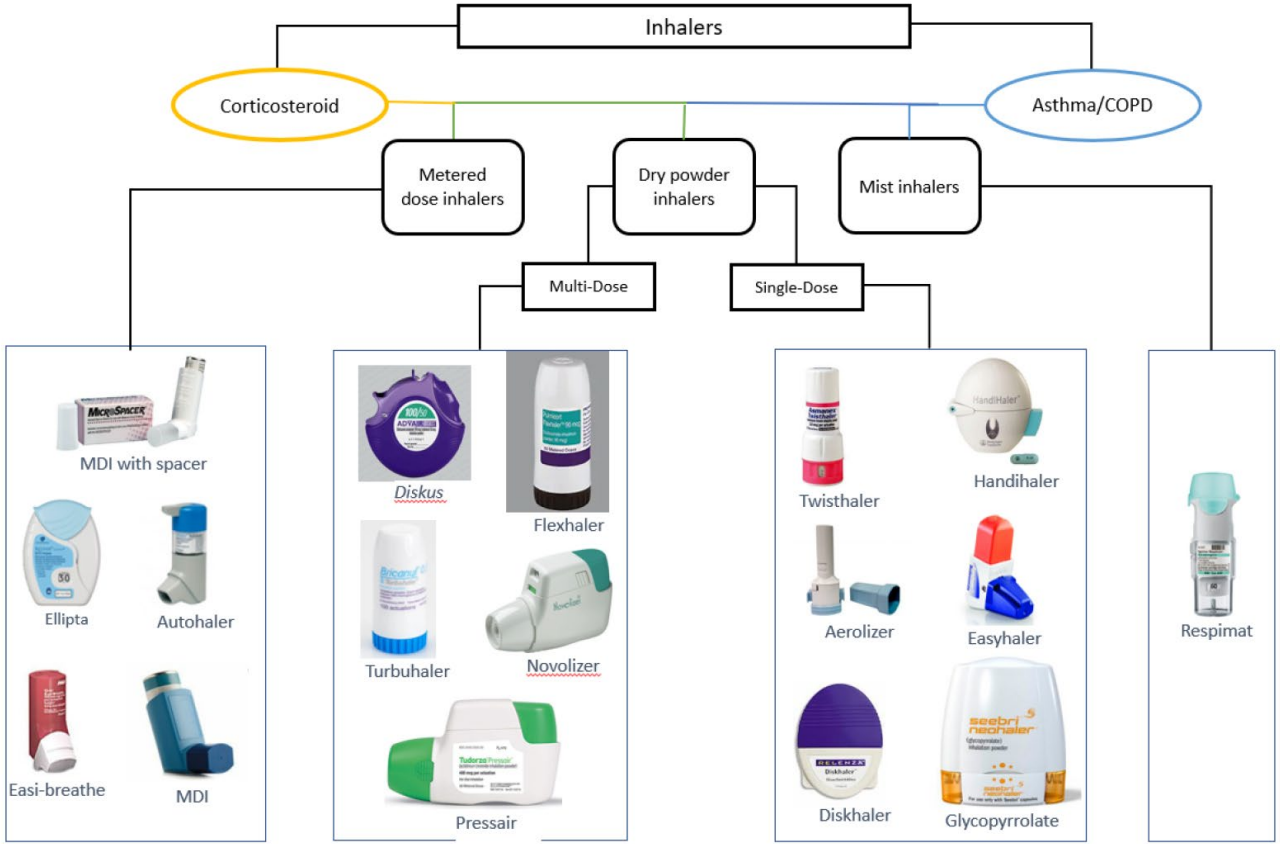
**Cap/ protective cover**

1. separate
2. tethered/ integrated
3. slide up cover

# Library of Inhalers by Design



# Library of Inhalers by Type



hs|d
A STERIPACK COMPANY

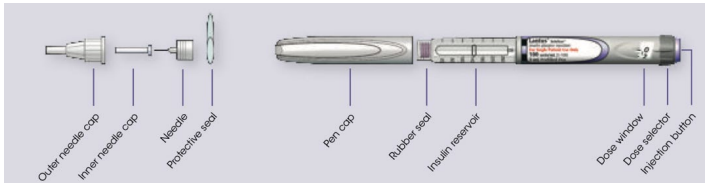
# GENERIC Examples Injection Pens / Pen Injectors

*Multiple use, adjustable dose, disposable*

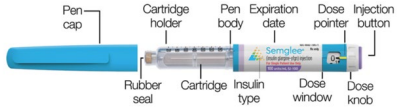
## Reference Listed Drug (RLD)

## Generic

**Sanofi:** Lantus (insulin glargine in SoloStar)

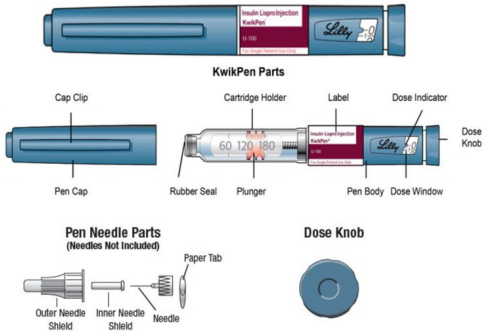




**Viatris:** Semglee (insulin glargine-yfgn in pen injector)

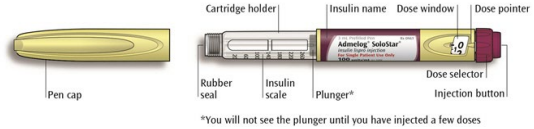





**Lilly:** Humalog (insulin lispro in KwikPen)




**Sanofi:** Admelog (insulin lispro in SoloStar)

# Possible Categories for Injector Library Classification

| | | | | | |
|---|---|---|---|---|---|
| Pen Injectors | Single-use | Fixed-dose | Disposable | | |
| | Multi-use | Adjustable dose | Reusable | | |
| Auto-Injectors | Single-use | Fixed-dose | Disposable | Button activation | Locking Mechanism |
| | Multi-use | Adjustable dose | Reusable | Needle Shield Activation | |
| Pre-filled Syringes | Safety Mechanism | | | | |
| | No Safety Mechanism | | | | |

hs|d
A STERIPACK COMPANY

# Our Research Continues….

Areas of exploration for CUHF Taxonomy development:

- Overall organization and categories
- Relationship with Use Related Risk Analysis
- Relationship with Root Cause Analysis

# THANK YOU

# Opportunities to leverage device functional assessment for classifying and evaluating user interface differences

GDUFA PUBLIC WORKSHOP | MAY 2022



BATTELLE

# Contents





BATTELLE

# Research Overview

- Generic device development is key to reducing the cost of medical care and increasing access to medications that will improve quality of life for many individuals.
- Current FDA guidance allows for an Abbreviated New Drug Application (ANDA) to be submitted for generic devices.
- Proposed generic devices are expected to be comparable in use to the Reference Listed Drug (RLD) without requiring HCP assistance or further training.
- Draft ANDA submission guidance suggests the use of threshold analyses to assess differences and use-related risks present between the RLD and the proposed generic combination device.
- Substantial differences may require additional human factors activities, such as CUHF studies to validate the differences.
  - Alternative approaches to CUHF studies are allowed by the agency for ANDA submission.

# Current Challenges

## ASSESSING DESIGN DIFFERENCES

- A threshold analysis is recommended to identify design differences.
  - In-depth guidance of this involvement is not outlined.

- Design differences must be categorized as ‘Minor’, ‘Other’ or ‘No Difference’.
  - Categorizations of differences may be challenging.
  - Design differences are considered ‘Other’ if differences in the UI may impact a critical design attribute that involves administration of the product.
  - Guidance remains vague on the meaning of ‘administration of the product.’
  - Some exceptions to labeling are allowed, however minimal guidance is given on allowable exceptions.

# Current Challenges

## COMPARATIVE USE HUMAN FACTORS STUDIES

- If 'Other' design differences are found, additional HF activities may be required, such as a Comparative Use Human Factors (CUHF) study.
- Submission of an ANDA where a CUHF study is needed can be time consuming and costly.
- Alternatives to the use of CUHF studies are allowed.
  - Current guidance does not specifically outline these alternative options.

# Opportunities for Research

Opportunities exist to further develop the guidance surrounding ANDA submissions.

- Clarification of the categorization of design differences is needed.
- Definition of which steps in the task analysis are required to be analyzed provide additional opportunity for research.
- Guidance on the labeling exceptions is needed.
- CUHF studies can be costly and time consuming and need more efficient alternatives.
- Incorporating use risk methodologies can provide additional data.
- Leveraging device functional assessment for classifying and evaluating UI differences may prove useful in finding suitable alternatives to CUHF studies.
- Internal mechanics provide additional opportunity for further functional assessment.

# Methodology Overview

Using existing human-centered design methodologies, a multi-step approach is proposed to conduct research that will provide more robust guidance for ANDA submissions of generic combination device products.

# Literature Search

- Conducting a literature search provides opportunity to assess where gaps exist in both guidance and research.
- Literature search results help to identify specific devices where research is inadequate.
- Keyword searches will include multiple search terms including:
  - Drug Delivery
  - Switching
  - Use Errors
  - Human Factors Research

# Product Selection and Evaluation

## PRODUCT SELECTION

- Careful selection is key to identifying appropriate devices.
- An RLD will be selected as a comparator for one or more generic devices.
- Devices are selected based on:
  - Applicability to the current market
  - Anticipated prevalence in the market
  - Limited published data currently available
  - Opportunity to fill research gaps using the selected device
- Devices selected are expected to have similarities in the user interface.
  - Devices may also have variable differences that will provide a variety of assessment opportunities due to the possibility of negative transfer.

# Product Selection and Evaluation

Two types of injection pens were selected for this assessment for the RLD candidate and generic devices.

### MANUAL INJECTION PEN

- Pen-like form factor
- User manually conducts all steps
  - Prepares device for injection (including selecting dose and priming device, if applicable)
  - Inserts needle into injection site
  - Depresses button to deliver drug by applying force throughout the injection

### SEMI-AUTOMATED INJECTION PEN

- Pen-like form factor
- User manually conducts all steps except dose delivery, which is automated
  - Prepares device for injection (including selecting dose and priming device, if applicable)
  - Inserts needle into injection site
  - Depresses button to actuate automated delivery of dose.

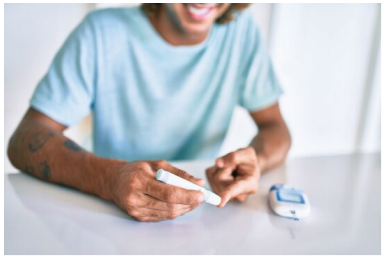
# Product Selection and Evaluation

## PRODUCT EVALUATION

A threshold analysis will be conducted using a variety of human factors and mechanical analyses.

### LABELING ANALYSIS

- IFU
- Packaging
- Device Labeling

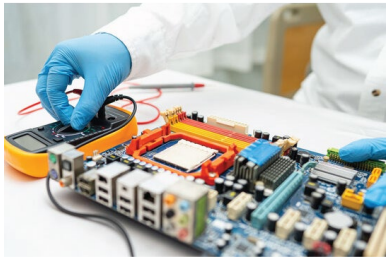


### TASK ANALYSIS & USE RISK ASSESSMENT

- Development and Comparisons

### PHYSICAL DEVICE ASSESSMENT

- Force Requirements
- Haptic Feedback
- Device Materials



### MECHANICAL TEAR DOWN

- Explore the relationship of inner mechanics to the UI.
- Not a requirement but may enhance guidance.

# Categorization Method Development

- Upon completion of product evaluations, device differences will be categorized.
  - Current categories include ‘No Difference’, ‘Minor Difference’ and ‘Other’.
- Alternatives to categorization can be explored.
  - Guidance needs to be clarified on categorization of ‘Minor’ or ‘Other’ differences.
  - Objective is to increase product safety and further streamline the ANDA process.




BATTELLE

# Assessment Method Development

- Design characteristics that fall under the categorization of ‘Other’ will require additional human factors activities.
  - CUHF studies are current primary method.
  - Alternatives to CUHF studies at this stage may now be explored.
  - Objective is to find more efficient methods to assess device usability.
  - Risk between the RLD and the generic combination device will also be assessed.
- Ideas for alternate methods of testing and evaluation will be identified for potential incorporation into guidance.

# Method Generalization

- Methods identified in previous steps will be generalized and documented to:
  - Expand the of breadth of applicability
  - Address identified gaps
  - Outline potential guidance to allow other entities to reduce the methods to practice.

# Conclusion

- Several opportunities exist to refine current FDA guidance.
- A multi-disciplinary approach will allow for enhanced methods for categorization and alternative methods for assessing ‘Other’ design differences identified.
- Research in this space will provide:
  - Streamlined guidance that will increase efficiency of ANDA submissions.
  - Speed time to market.
  - Allow for greater public access to generic combination device products.

# Thank you

Hailey Fehrenbach, MS
Industrial & Human Factors Engineer
fehrenbach@battelle.org

# Insufficient Published Literature Related to the Usability of Device Constituent Parts

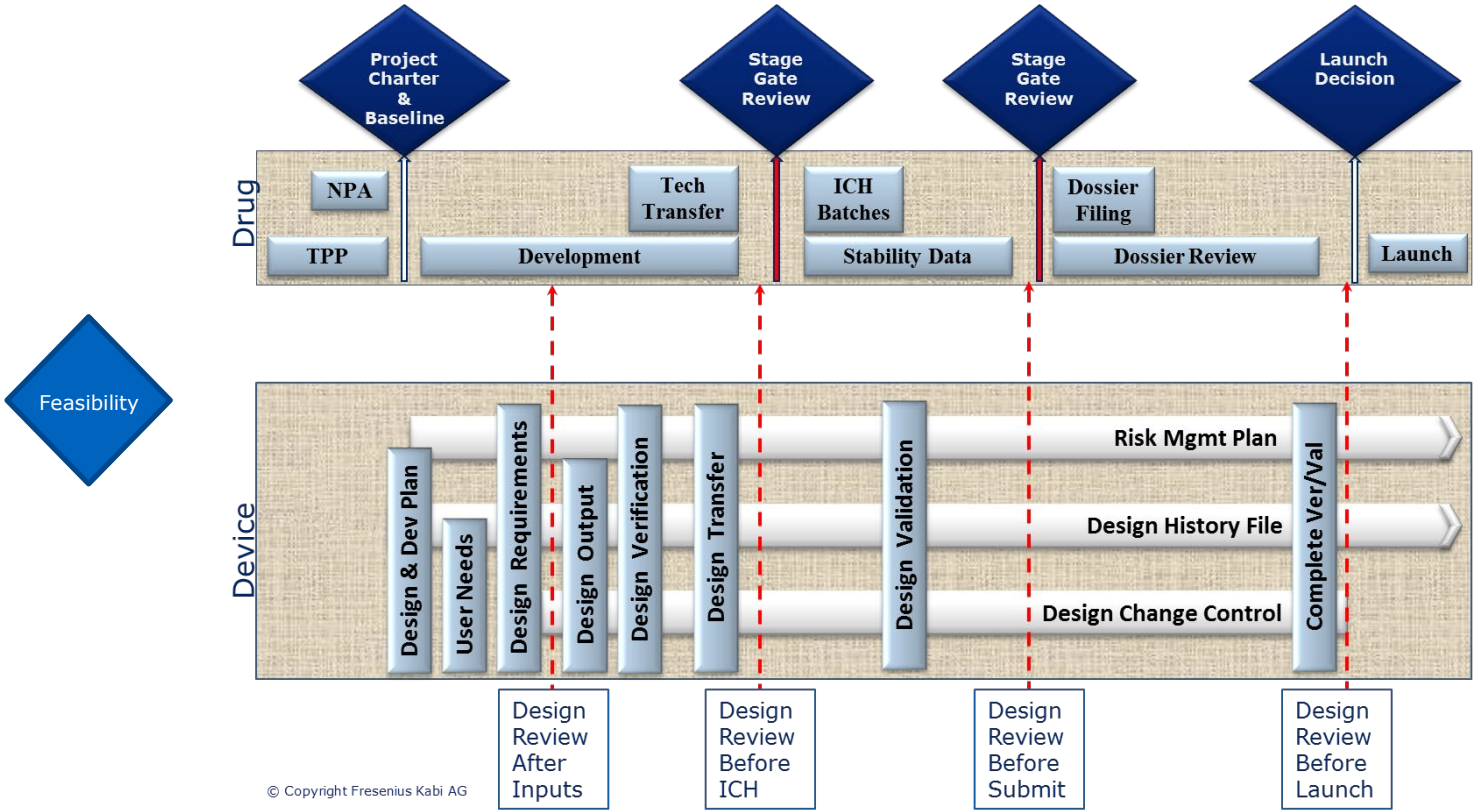
Tracy VonBriesen , RN, MS
Director, Clinical Development

**The goal of my presentation is to provide and example of the gap in the published literature related to device constituent parts**

**Why is the published literature so important?**

- Used throughout product development
  - Feasibility
  - Risk Management activities
  - Helps support design requirements with clinical/ end user context

# Linkage Design Controls - Drug Development Process



# A PubMed search was performed with these key words in different combinations

| Terms | Number or results |
|---|---|
| Pen Injector | 89 |
| usability AND pen injector | 11 |
| Human Factors AND pen injectors | 14 |
| Validation and pen injector | 9 |
| Auto injector | 900 |
| Autoinjector AND human factors | 39 |
| summative testing AND Injection pen | 8 |
| Autoinjector AND usability | 43 |
| Summative testing AND autoinjector | 4 |
| Validation and autoinjector | 55 |
| Platform autoinjector | 10 |
| Platform pen injectors | 2 |
| Total | 1,184 |

Inclusion Criteria

- Related to usability of the device
- Less than 10 years
- English
- US based study

Total publications that met the inclusion criteria: 44

## Real World Use

Majority of the publications reported subjective data

- Satisfaction levels
- Ease of use
- Confidence levels regarding self injections

## Human Factors Engineering Testing

Synthesized objective data

- Task analysis
- Use errors, use difficulties, close calls
- Root cause analysis

## Post Market Human Factors studies

Comparison of same drug different device

- Post hoc analysis for new indications for use
- Objective/subjective data
- Not always powered to demonstrate superiority
- Ease of use
- Patient preference

## Human Factors Engineering Lab Testing

Provides objective laboratory testing that can be used to support design requirements

- Measurements of applied forces

# How can FDA support the combination product development for ANDA products from a literature perspective?

I would like to propose that the FDA works in collaboration with professional organizations that focus on patient safety and usability of combination products such as ISMP, National Patient Safety Foundation to conduct human factors studies and publish the results so that the data can be applied consistently across manufacturers and establish appropriate design requirements.