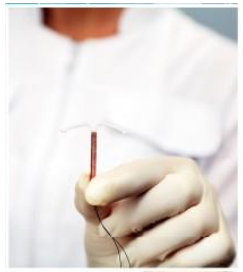
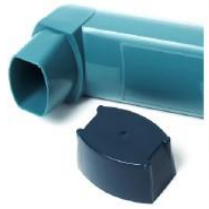




Drug-Device Combination Products Workshop: Updates & Challenges with Demonstrating Generic Substitutability

U.S. FOOD & DRUG ADMINISTRATION

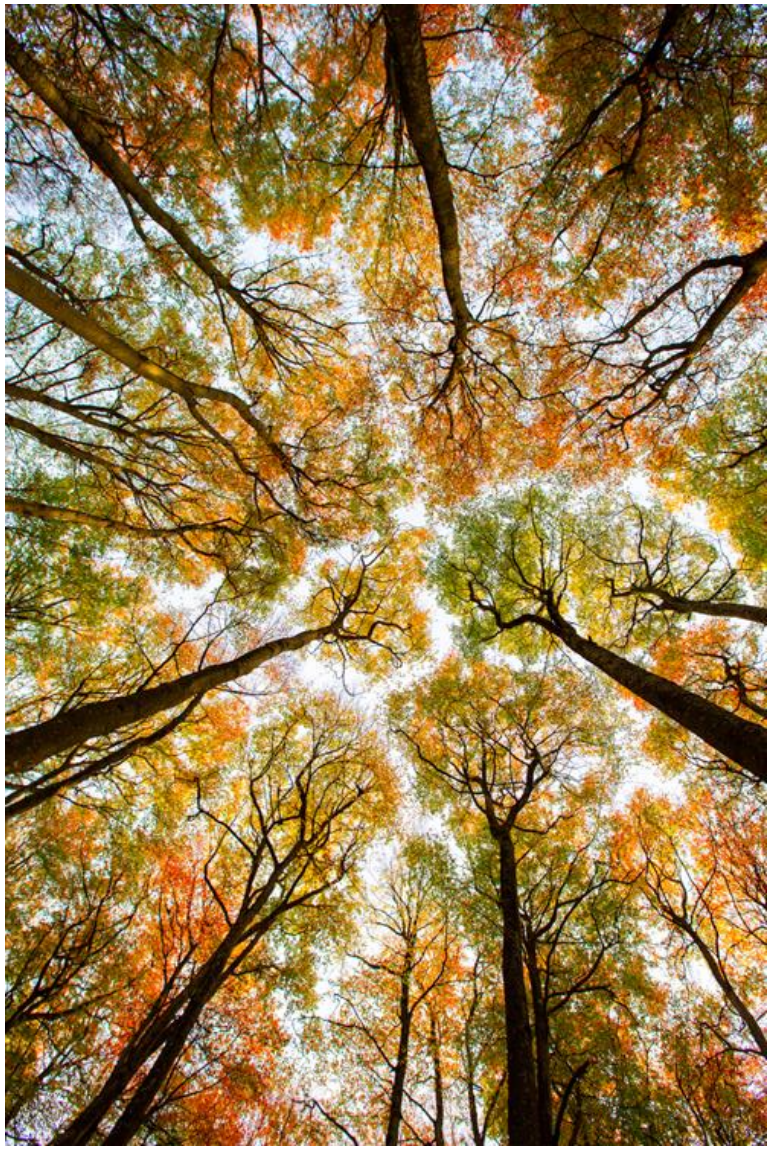
CENTER FOR RESEARCH ON COMPLEX GENERICS

Symposium III:
Setting the Course for the Generic DDCP Future

Katharine B Feibus, MD
Lead Physician/Team Leader
Device Evaluation Team
DTP-I, ORS, OGD, CDER, FDA

Purpose/Goals of Symposium III

- Share challenges in pursuit of a better future state
- Share ideas and possible paths forward to inform further discussion, work, research in this area
- Not developing new FDA policy or guidance at this workshop



Symposium III: Setting the Course for the Generic DDCP Future

Topic 1 (Room 1042):

Minor Design Differences vs. Other Design Difference – Learning to Speak the Same Language.

Facilitators: Betsy Ballard, Lee Leichter, Mary Beth Privitera

Topic 2 (Ballroom):

When Might "Other Design Differences" Be Justified Without a CUHF Study?

Facilitators: Irene Chan, Michelle Lin, Claire McDiarmid, Heidi Mehrzad

Topic 3 (Room 1032):

Designing and Executing CUHF Studies – Choosing Study Population(s) and Statistical Methods

Facilitators: Tim Briggs, Somesh Chattopadhyay, Jason Flint, Tom Gwise

Topic 4 (Room 1052):

Building a More Informed and Flexible Comparative User Interface Assessment Landscape

Facilitators: Stella Grosser, Markham Luke, Satya Patil

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To Our Facilitators and Participants:

Ongoing Outcome-Related Activities

- FDA and CRCG will stand up a CRCG working committee that will collaborate with FDA to develop a Generic DDCP Comparative User Interface Roadmap and plan and prioritize next steps and research questions to address and bridge the gaps identified during this Symposium.
- There may be opportunities for interested facilitators and workshop attendees to participate in the larger CRCG working committee or in subcommittees established to work on specific gaps and challenges identified in this symposium.
- Information shared and ideas developed during this symposium will initiate a work plan to prioritize and address gaps in resources and scientific knowledge that can inform committee work, FDA-funded research, and potentially future guidance and policy related to DDCP user interface assessment.

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And to our AMAZING working session notetakers…..

- Joyce Chen, Pharm D
- Shinae Kim, PhD
- Karthika Natarajan, PhD
- Johnny Nguyen, Pharm D
- Yeong Seo, Pharm D

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Topic 1:

Minor Design Differences vs. Other Design Difference – Learning to Speak the Same Language

Co-facilitators:

Mary Beth Privitera, MDes, PhD

Betsy Ballard, MD

Lee Leichter, RAC, MBA

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How to describe design differences?

- Hire a design firm- Critical task decision-making poses challenges intermittently. Simultaneous independent risk analysis and task-based analysis. Justification of decisions is crucial; both the how and why they are vital
- Develop a set of design attributes based on RLD
- Identify that CANNOT be innovated (patent issues, etc)
- Develop various versions of the design and tabulate the differences using a design decision matrix
- Formative CUHF study
- Define critical tasks- use URRA
- Use off-shelf components/devices
- Have 2 different people assessing the design then comparing answers

Common issues: describing design differences

- Can be subjective assessment
- Not a simple process
- Reliant on off the shelf components (OEM)
- Defining critical risks of the RLD

Determining Minor vs Other

- Debate

Common Issues: Minor vs Other

- Tying design to [critical] tasks is a challenge
- Defining Critical Task
  - Update caused more confusion
  - Everything is minor until otherwise…
- Defining compromised medical care is difficult
- Uncertainty around categorization

Ideas

- Need to have a standardization on how categories are performed
- Publicly available referenced database
  - Include the context of use (user population, context of use, location, co-morbidities/impairments)
- Incorporate URRA into design comparison
- Give examples of best practices – published
- Develop a database of RLDs & specific contexts that can be used to create a matrix system using FDA submitted data (redacted- of course)
- Define what data is acceptable as a determination of minor vs other & publish this
- Provide examples of ”other” design differences that have been approved and how they were justified
- Develop a tool to conduct design analysis

SYMPOSIUM III TOPIC 2:

When Might "Other" Design Differences be Justified without a CUHF Study?

CAPT Irene Z. Chan, Pharm.D.
Deputy Director
OMEPRM, OSE
FDA

Michelle Lin, M.D.
Senior Physician
DCR, OSCE, OGD, CDER
FDA

Claire McDiarmid, M.S.
Senior Director
User Interface and Risk Management
Global Device Development
Viatris, Inc.

Heidi M. Mehrzad, EMT, M.S.
CEO, Founder and Consultant
Human Factors and Usability R&D
MedDev and Combo Development
HFUX Research, LLC

Surveying the Room, Participants were Asked…

What their drivers for attending this session and what they were interested most to learn from it?

- Make sure we are conducting CUHF correctly
- What is changing regarding DDCP
- Learn about “Other” differences, how to approach, how to test it
- Share experiences and explore options
- Increase confidence of doing something other than CUHF
- How to derive at other approaches
- Parameters around CUHF: cost and time
- Encounter ‘Other’ design differences
- Understand peers’ challenges across the field
- Align/find consensus in language used
- Learn about alternatives to CUHF

Why would they want to seek alternatives for a CUHF study?

- To meet customer timelines/requests
  - ➢ off the shelf device manufacturers -> pharma companies
- To potentially save time and cost
- To understand why CUHF is needed when alternative data is available (data provided was not accepted by FDA)
- To commercialize DDCP faster and/ or at all

Workshop Exercise:
Context Questions to Consider

Example Context Questions

- Is the product being used in an emergency use vs. chronic use scenario?
- Who are the users?
- Where would the DDCP be used? What is the environment of use?
- Regarding risks: Did the drug product (drug constituent part) have a narrow therapeutic index?
- What are the potential use errors for this difference?

What type of information/data may support this type of difference?

- How would you apply this information/data?
- Why do you think this is scientifically supportable?
- Would this apply to all use scenarios and all user groups?
  - e.g., emergency vs chronic use, adult vs pediatric population
- Are there other considerations that we should account for?

Summary: Examples Mentioned

1) Resetting Button (proposed generic does not need reset)
2) **Extension of Dose Button**
3) **#of Activation Use Steps (Autoinjector)**
4) **Different Graduation Marks**
5) Different Color Coding (of graduation marks/ or device overall)
6) **Autoinjector -> PFS**
7) **Pen Injector – Pull Push vs Push or Slide Button**
8) Pen Injector – Change Steps to Dial Dose
9) **Autoinjector – Cap vs. No Cap**
10) Pen Injector – Different Locking Mechanism (avoid accidental injection)

Key Takeaways

1) **Context is IMPORTANT**
   - Any of the Examples mentioned could have been “Other” design differences
2) **Use-Related Risk Should be Key Driver in Strategy Selection -> for Alternative Approach**
3) **Considering Multiple Types and Sources of Data or Information to Support “Other”**
   - Providing Comprehensive and Cohesive Story for FDA to Follow your Reasoning for Classifying a Difference as “Other” and Corresponding Data Provision
4) **Can a 2-Arm Human Factors Summative (Validation) Study be Used?**
   - In Some Cases: Summative + Residual Risk Analysis Could Suffice
   - Depending on Results of Summative next Steps may Include:
     - ✓ Re-Design User Interface
     - ✓ Collect Additional Data, e.g., CUHF
5) **Interest in Exploring How Clinical Data, Real-World Data, and/ or Adverse Event Reporting Could be Used to Justify an “Other” Difference**
6) **Can You Rely on Someone’s Data or Other Data Out There?**
   - **Would that Present Legal Challenges/issues?**

Summary: Detailed Table Discussion Findings

Extension of Dose Selection Button

- Impacts multiple tasks: (1) Selecting dose, (2) administration
- One consideration is looking at device performance: Under-dial vs. Over-dial
- Anthropometric/Biomechanics data – studies on hand strength, breaking down movement into subsystems are available
- Depending on the task/risk assessed, may still need CUHF study
- What are specifics of data that's important?
    - Sample size, study design, etc.
- FOIA Review/Study Data on Similar Device
- Is post-marketing data meant to answer regulatory questions around substitutability.
    - What about real world data on safety?
- Looking at public medication error data
- Available clinical data error may demonstrate that the difference does not impact risk.

#of Activation Use Steps (Autoinjector)

- RLD has 4 steps vs 2 steps generic.
- If same use scenario & same user representation, then using other supplemental data such as:
    - Rely on another ANDA's approval that evaluated similar scenario
    - Could there be a research project in this space (BAA)?

Different Graduation Marks

- Need to take into consideration the End-user (HCP vs Patient vs Caregiver)
- Patient age perspective with the cognitive abilities (adolescent, caregivers, senior)
- Disease state could impact reading of graduation marks (diabetic, vision)
- Other co-morbidities that could impact the use of reading the graduation marks.
- Looking at public data available with similar generic products on the market
    - Depending on white paper, with some caveats
- Using biomechanics/anthropometric data
- Data gathering to power statistical study to specifically look at this attribute and gather data on negative transfer
- Fill in the gaps with other data (supplemental data) to justify this "other" design difference
- Use theoretical sampling in respect to not do a CUHF study. Have your parameters set and structured to see if it was employed in real life, there's a strong confidence you'd see the same result in the real-world setting
- Public available data
- Rigorous formative study
- Supportive data built on the risk analyses.

Summary: Detailed Table Discussion Findings

Autoinjector to PFS

- Considerations: cost, dose window, plunger vs. button to administer dose, training, feedback when injection done, needle gauge and length
- Alternative approach: existing real-world data, validation study, performance study, biomechanical data (rate of dose delivery and force)

Pen Injector – Push Pull, Push, or Slide Button

- Depends on the context of use -> URRA
- If it improve the user interface, CUHF study may not be required
    - Analytical data (e.g., in vitro study) to support the "improvement"
- Alternative approach: validation study (recruit existing user, results help inform next step:
    - Residual risk study for informing decisions regarding safety and usability.

Autoinjector – Cap vs. No Cap

- Cap vs. no cap (Lack of task steps) : assumption is the RLD has a cap, while the T has no cap
- This design difference for the emergency use product will be an "Other"
    - But if it's a standard and chronic use product, it can be "minor" depending on the context of use (environment, patient population)
    - **Note:** that there will be a learning effect (1st time will takes more time to figure out for proper use, but will reduce the time of delay) with assuming any training is not provided for the patient (illustrated instructions will be helpful)
- Use error –device damage and patient harm (needle stick).
- Alternative approach:
    - 2-Arm study between the focusing group of RLD used vs. naïve. If see risk, the validation study can be a steppingstone for the next step (whether will be go the CUHF study or not, or redesign)
    - Real world/published/adverse event data to show the safety data
    - Heuristic analysis informing URRA

Designing and Executing CUHF Studies

Thomas Gwise, PhD, Principal Statistician, T Gwise Consulting LLC

Tim Briggs, Senior Principal Human Factors Engineer, Viatris

Jason Flint, MBA, PMP, Deputy Director, CDER/OSE/OMEPRM/DMEPAI

Somesh Chattopadhyay, PhD, Lead Mathematical Statistician, CDER/OTS/OB/DBVIII

CRCG March 14-15, 2024, workshop
"Drug-Device Combination Products: Updates and Challenges with Demonstrating Generic Substitutability".
Symposium III – Topic 3

Agenda

- Introduction and Ground Rules – 10 minutes
- Overview of HF and CUHF – 15 minutes
  - HF and CUHF compare and contrast
- Topic 1 –Non-inferiority design 15 minutes
  - Reform/Adapt Non-Inferiority design
- Topic 2 – Qualitative designs 15 minutes
  - Reform/Adapt qualitative approaches to confirm substitutability of a proposed generic
- Topic 3 – Alternative designs 15 minutes
  - Identify other methods to confirm substitutability of a proposed generic

Ground Rules

- Be courteous and respectful
- Be an active participant
- Focus on the future state
  - Raise challenges, but propose approaches to address them
- We are not making policy
- Other ground rules from the participants?

Overview

Human Factors and Comparative Use Human Factors Study Designs

CRCG March 14-15, 2024, workshop
"Drug-Device Combination Products: Updates and Challenges with Demonstrating Generic Substitutability".
Symposium III – Topic 3

Qualitative Human Factors Study Design

Assess adequacy of the device user interface (UI) in consideration of **safe and effective use**.
Typically, **non-comparative**.

- Identify intended users
- Identify safety related tasks (Critical Tasks) and Essential tasks
- Identify user interface risk controls.
- Develop success/failure criteria for each task.
- Select a sample size large enough to detect user interface design issues if they exists.
  - Typically, 15 – 20 per user group
  - A sample of 20 is sufficient to find a minimum of 95% and an average of 98% of problems[1].
- Any use task performance that fails to meet the defined success criteria – use errors, close calls, use difficulties is recorded and analysed to determine the potential root cause.
- If issues are identified - assess if design changes are required i.e. could failure be mitigated with an updated design?

[1]Faulkner (2003)

Comparative Use Human Factors Study Design

NI Study Design

- Goal
  - Show that differences in device do not impact sameness
- Steps
  - Assess risk of observed differences
    - Threshold analyses
  - Determine how much inappropriate use is untenable
    - Margin (d)
  - Collect Data
  - Test
    - H_0: T-RLD >= d
    - H_A: T-RLD < d

Example: Compare rates of inappropriate action

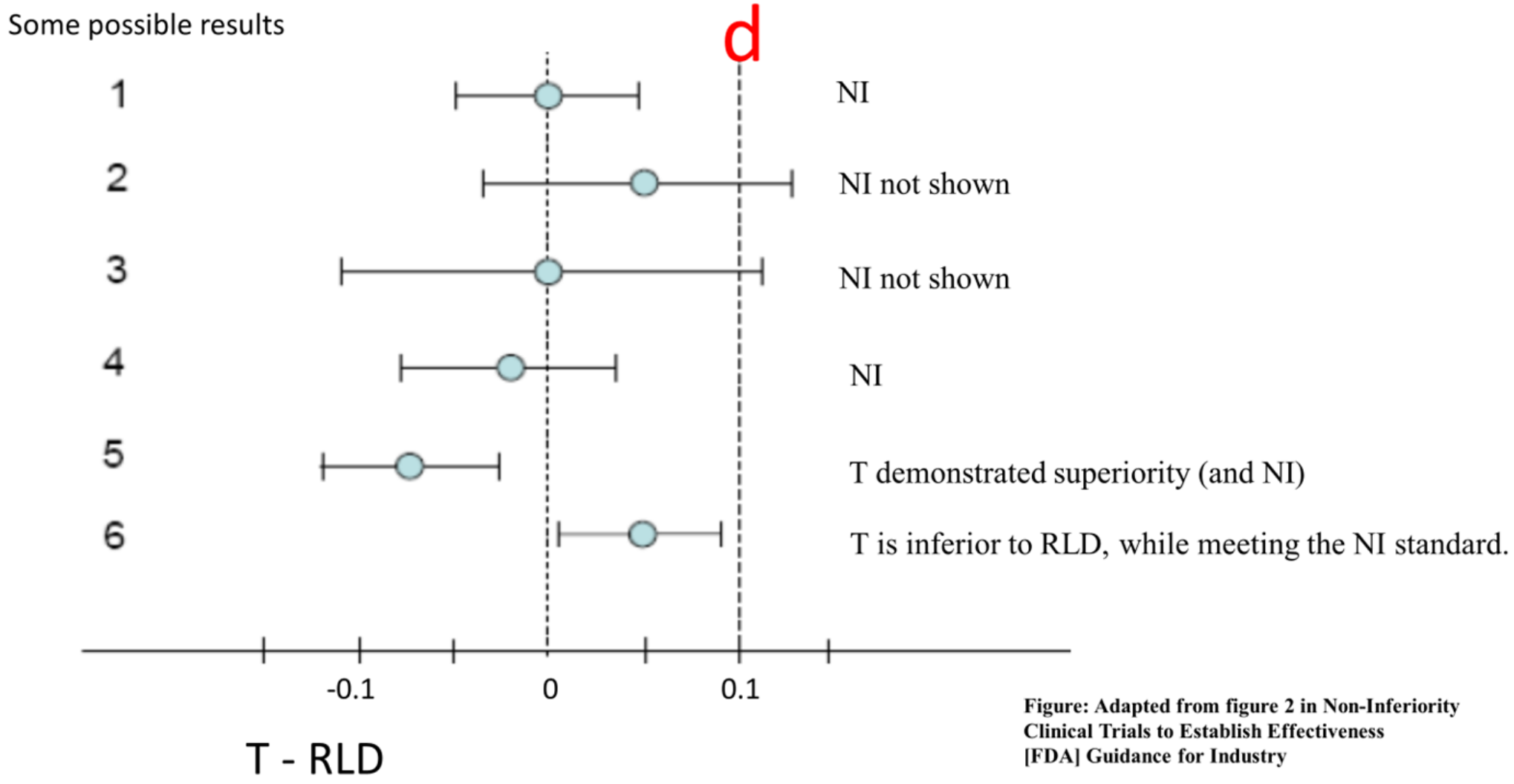

Figure: Adapted from figure 2 in Non-Inferiority Clinical Trials to Establish Effectiveness [FDA] Guidance for Industry

Topic Area 1 Non-inferiority CUHF Design

- Setting the Margin
  - Available data
  - Risk-based
  - Explore assumptions –
    - RLD error of 0
    - Pilot study
  - Fixed margins based on risk “buckets”
    - Different “buckets” based on risk e.g. Chronic v Emergency use
- Clarify Error Definitions – study specific (could potentially include learning)
- Continuous vs Binary outcomes
  - Magnitude of dose errors as one example

Topic Area 2 Qualitative HF Designs

- Goal – Demonstrate substitutability of a proposed generic
- Experienced RLD users and Naïve users
  - Large enough sample size to detect errors
  - Root Cause Analyses
    - Why are errors occurring?
    - Negative Transfer?
    - Unique between RLD and Proposed generic?
    - RC linked to differences?
  - Demonstrate low risk of difference in clinical effect and safety profile
  - Could be comparative?
- Approach may be predicated on use of the HFE process throughout

Topic Area 3 - Alternative designs to demonstrate substitutability of a proposed generic

- Goal – Demonstrate substitutability of a proposed generic
- Quantitative NI design with fixed assumptions
- Hybrid Qualitative/Quantitative
  - Errors as magnitude of dose difference + existing clinical data
  - Demonstrating that UE would not lead to a clinically meaningful difference
- Modeling – Brief discussion, but generally not seen as a good option due to complexity
- Bayesian Approaches – Brief discussion but may have similar challenges
  - Determining the informative prior
  - Still need to determine d

Backup

Qualitative **Comparative** Study Design??

Assess adequacy of the device user interface (UI) in consideration of **substitutability**.
Comparative study design (Paired AB/BA)

- Identify intended users **incl. users experienced with reference product.**
- Identify safety related tasks (Critical Tasks), Essential tasks **and tasks potentially impacted by design differences.**
- Identify user interface risk controls.
- Develop success/failure criteria for each task.
- Select a sample size large enough to detect a user interface design issues if they exists.
  - based on a set of assumptions regarding: a fixed (and known) probability of encountering a problem, a uniform likelihood for each participant to encounter each problem, and the independence of the problems (that is, encountering one problem will not increase or decrease the likelihood of finding other problems).
  - Typically, 15 – 20 per user group
  - A sample of 20 is sufficient to find a minimum of 95% and an average of 98% of problems[1].
- Any use task performance that fails to meet the defined success criteria – use errors, close calls, use difficulties is recorded and analysed to determine the potential root cause.
- If issues are identified – **assess if issues are comparative**, assess if design changes are required i.e. could failure be mitigated with an updated **more comparative** design?

[1]Faulkner (2003)

Symposium III

Setting the Course for the Generic DDCP Future

March 14-15, 2024

Topic 4:

Building a More Informed and Flexible Comparative User Interface Assessment Landscape

Facilitators: Stella Grosser, Satyashodhan Patil, Markham Luke

Current state and challenges – Session 1

Comments

- FDA limited by regulation and Supreme Court and also not with clear guidance.
- New Drug industry is biggest lobbying group in US.
- Policy documents are outdated.
- FDA not meeting expectations on labelling.
- DDCPs are difficult to copy because of patents.
- Difficulty on to figure out critical differences.
- Litigations on RLDs
- AI role in using current database in an unbiased way.
- Problem with orange book.
- Industry unlikely to share data.
- In CUHF study, challenges related to sample size, determination of NI margin. Generic industry struggling to demonstrate substitutability.

Discussion

- Whether smart devices creates barriers to generics?
- What would it look like to grant more flexibility?
- Could the FDA be more explicit on what type of flexibility might look like?
- What are the ways that would loosen up? In measuring these things in the post-marketing setting, what would the flexibility look like?
- If FDA could have Congress change something tomorrow what would that be?
- There is a perception that CUHF studies are the end all be all in?
- If we are thinking about post marketing studies and how to get generics on the market, like generics getting pulled a coupled years later because they do not work?
- How should we consider when patients cannot afford the product so there is a need for generic?

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Current state and challenges – Session 2

Comments

- Syringes of different designs can lead to medication errors. Better access to drugs that are off-exclusivity and are DDCPs
- Existing patent landscape and problems that affect access to generics.
- Insurance companies or Payors instead of FTC taking up claims related issues with DDCPs
- In vitro testing is an evolving process but there is still space for research and development and guidance for implants and intravaginal rings and for microneedles and iontophoretic systems in the future.
- There is no prescriptive guidance for PFS compatibility with reusable autoinjectors that are reused but the PFS is replaced by the patient for each use e.g., Capoxone. Current standards are very high level and more specific technical consideration guidance will be helpful.
- Current CDRH regulations are broad and not very specific

Discussion

- There is current ongoing work on categorization of various inhalation products in CDER
- CDRH has guidance for nebulizers and spacers for general inhalation
- CDRH - general control for a nasal spray device
- CDER - provide design controls when systemic delivery of drug is desired and more controls are needed
- Discussion on Class I, Class II and Class III devices, special controls, downgrading and upgrading devices
- Definitions for ocular syringes and on body injection systems were developed in CDRH recently? Similar definitions will be helpful for all types of devices

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Desired future state – Session 1

Ideas

- Early conclusion from FDA, in other words, a quick review
- Substitutability Software app in public domain
- Legislation need for patents
- Use of standards for regulation of new and generic drugs
- Mathematical app for demonstrating substitutability driven by data science and Artificial Intelligence
- Risk to environment of risk-benefit analysis for approval of generics
- Balance of risks of differences and risks of not approving
- Public investment by Congress
- Ability to leverage prior experience is key
- Machine learning to validate legal claims and patents
- Machine learning to compile research, assess if differences are statistically significant in the context of the target user demographic.
- Compile relevant research and data.
- Cooperation and collaboration to address differences as multiple companies use the same platform.

Discussion

- The generic industry cooperates for REMS – they cooperate with each other and come up with consortium to monitor all generic drugs out there on AE's and prior authorization. In the DDCP space, there is room for collaboration especially for smaller generics and combined efforts. Is there a problem with sharing like can it be seen as collusion? For REMS program, FDA acts as the mediator, we facilitate conversation. Can we do that for this so that generic companies are not seen as colluding?
- Can there be a DMF for the pen?
- Can the safety assurance case method be used?
- Include AI tools for post-marketing surveillance?

Desired future state – Session 2

Ideas

- Identify current data that exists to support one device is equivalent to another.
- Industry standards for markings would be helpful.
- Take advantage of the pre-ANDA program – early interaction
- GDUFA III – more space for interactions
- Interest in standardization in standards and guidance specific to DDCPs' that include device evaluation
- Specification clear on label.
- Most common design changes – two step approach
- Clarify on study designs for the CUHF study approach.
- No CUHF study only comparative assessment
- Multiple strengths of the same DDCP – consider a single ---CUHF study at least for the same device model (fixed vs variable pen)
- Increase period of exclusivity for first to file DDCP generics – congressional decision with justification for a public health need

Discussion

- What would be required for a Vial to PFS - full HF validation study? Will it meet ANDA requirements or 505 B2 is the only pathway?
- Glass PFS – generic is trying to be better with an integrated needle safety system. -what is the activation force? No reference.
- Verified and validation- how to validate when the RLD has no safety system?
- Some allowable changes for the generic compared to RLD in terms of improved patient safety – develop standards as needle stick prevention is important
- RLD is withdrawn – consider allowing differences
- When multiple generic companies are trying to bring similar platform or there is a standard platform then FDA assess the test against RLD and publish the data or use that data to accept the generic without the need for CUHF studies?
- When both RLD and Test meet ISO standards then is comparative assessment needed?

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Current resources and opportunities & Other needed data or resources

Current resources and opportunities

- FDA must be with huge data on several types of devices from innovator and generics.
- Data from FDA , generic industries and research institutes can be utilized to build streamlined framework for demonstrating generic substitutability.
- Resources at FDA, academics and generic industries can collaborate together for research opportunities to generate the data.

Other needed data or resources

- Funding from FDA or generic industries for joint collaboration on research topics.
- ISO standards – not prescriptive and allows for flexibility
- FDA can be more prescriptive and provide technical details more than ISO
- Support from FDA and ISO organization for more clarity on standards.
- Set up standards for general use for specific device categories

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Thank You