An FDA Perspective on Best Practices for Comparative Analyses: Challenges & Opportunities

Katharine B. Feibus, MD, Lead Physician Device Evaluation Team
DTP I, ORS, OGD, CDER, FDA
CDR Andrew Fine, PharmD, Senior Advisor
DCR, OSCE, OGD, CDER, FDA
Jason Flint, Deputy Director
DMEPA 1, OMEPRM, OSE, CDER, FDA

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Objectives

- Understand Comparative Analyses (CA) Process and key players during generic user interface assessment
- Emphasize CA foundational principles and best practices
- Discuss other design difference challenges and when a Comparative Use Human Factors (CUHF) study may not be required
- Highlight CA challenges and strategies when the Reference Listed Drug (RLD) is discontinued

Comparative Analyses (CA) Process

Overview and Key players

Key Players

OGD Division of Therapeutic Performance I (DTP I)

- Lead for pre-ANDA CA assessments

OGD Division of Clinical Review (DCR)

- Lead for ANDA and post-approval CA assessments

OSE Division of Medication Error Prevention and Analysis I and II (DMEPA)

- Lead for CUHF Study protocols and assessments

Office of Biostatistics, Division of Biometrics VIII

- Statistical lead for CUHF study assessment

The comparative user interface assessment process is a cross-Office, collaborative CDER process. Our groups work together on CA and CUHF study issues throughout the ANDA lifecycle.

Photos by John Nguyen, Pharm D, ORISE fellow

CA Process in Pre-ANDA Review

Pre-ANDA CA Process: OGD DTP I

- Specific user interface questions
- Comparative analyses (all 3)
- Samples of RLD and proposed generic
- Send Information Request (IR) if needed

Submission sufficient for evaluation?

Review and perform CA between RLD and generic device user interfaces

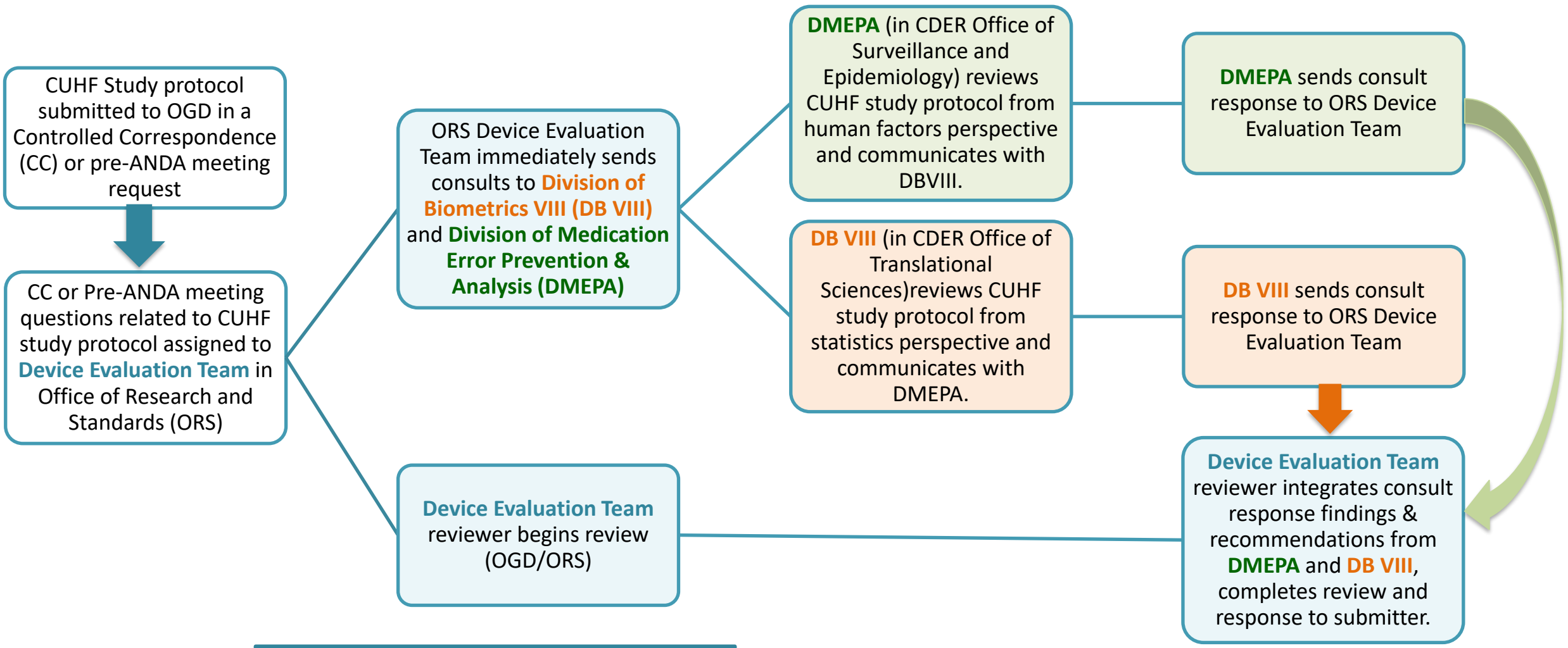
- Review firm's submitted CA
- Perform independent CA
- Compare findings
- Complete review with draft responses to submitter (2-3 levels of review)

- Obtain input from DCR (or DMEPA):
  - If unclear whether a design difference is likely to be viewed as "minor" v. "other," during ANDA review
  - To see if a particular other design difference has been viewed as "acceptable" without additional data or information. Applicable to this product?
- Finalize review and response to submitter

Develop and send response to submitter

Review timeline is 60 days (CC) or 120 days (pre-ANDA)

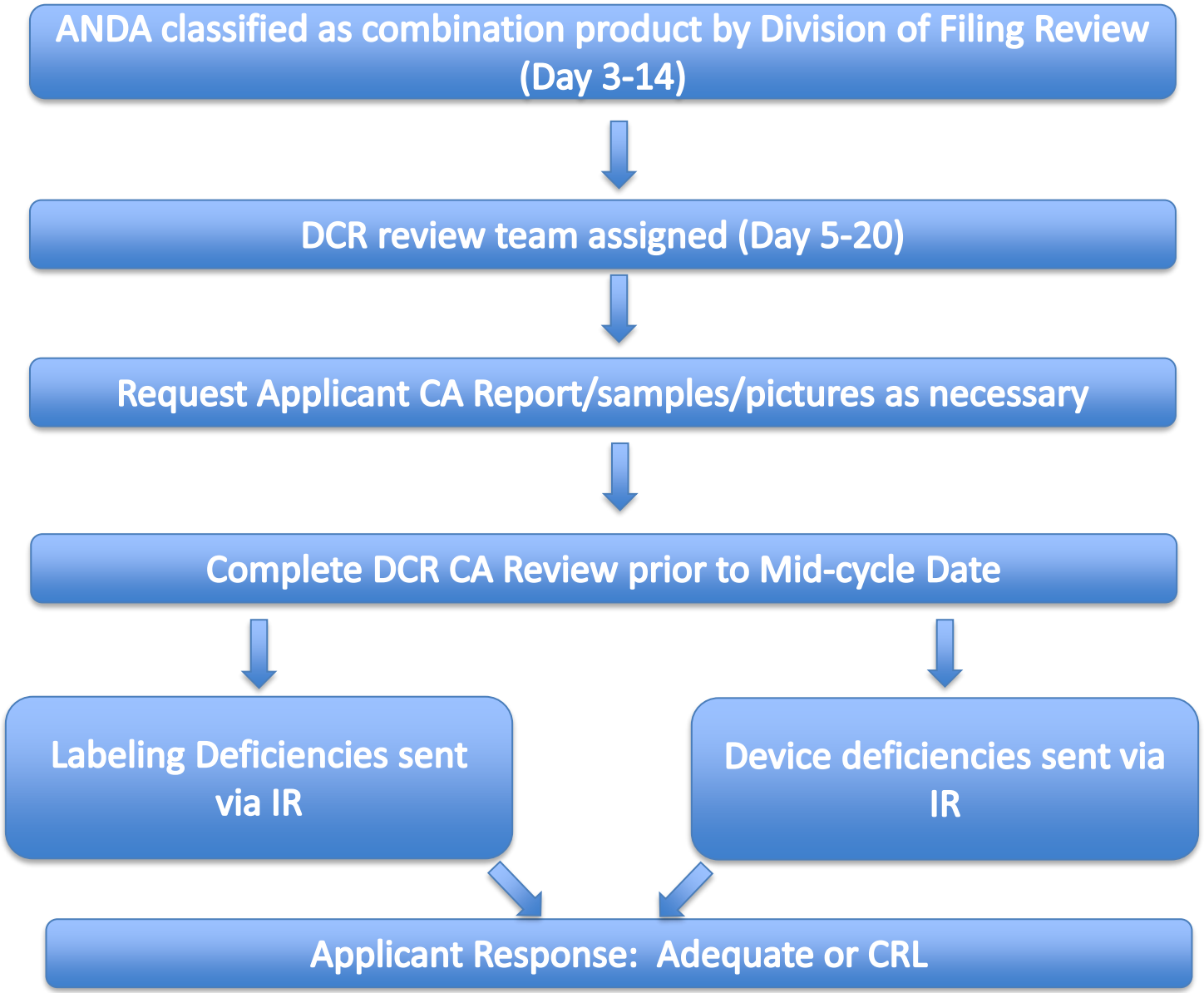
Pre-ANDA Submission: CUHF Study Protocol



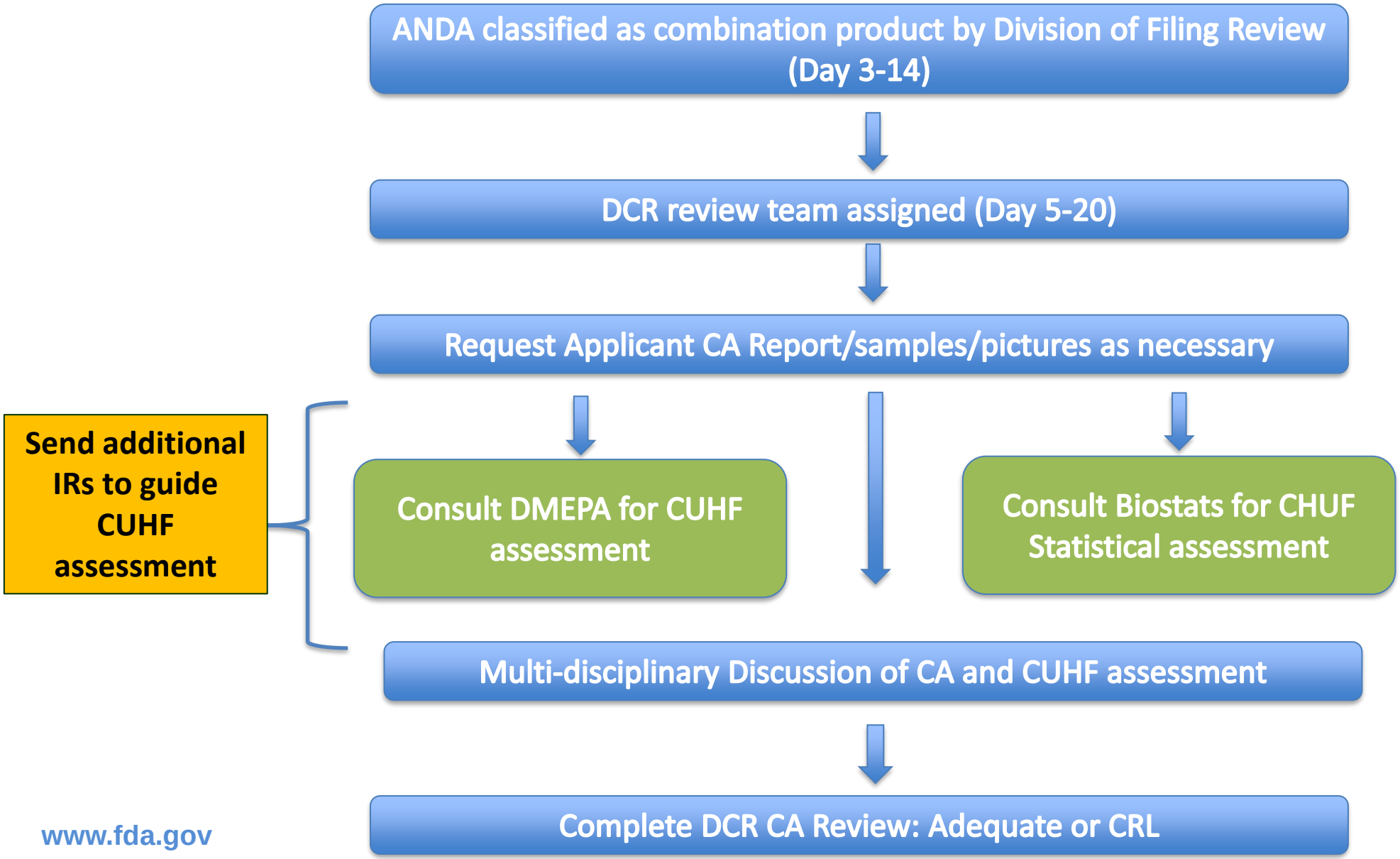
Review timeline is 120 days

CA Process in ANDA Review

CA Review Process for Original ANDAs



CA Review Process for Original ANDAs with CUHF



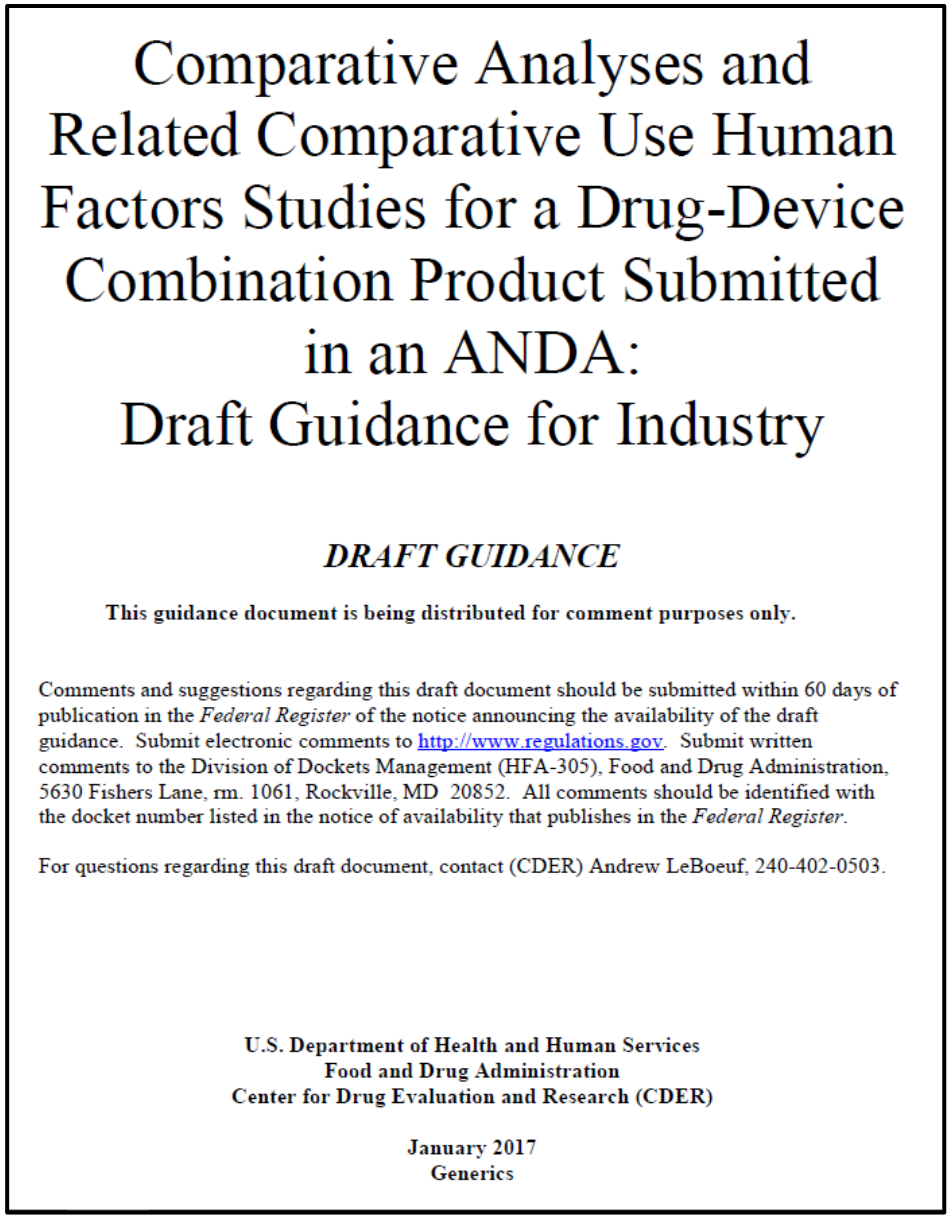
CA Process: Foundations and Best Practices

Generic Drug Products: Regulatory Framework

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

FDA Draft Guidance "Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA"
https://www.fda.gov/regulatory-information/search-fda-guidance-documents/comparative-analyses-and-related-comparative-use-human-factors-studies-drug-device-combination

Draft Comparative Analyses Guidance



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

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Andrew LeBoeuf, 240-402-0503.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

January 2017
Generics

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

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

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

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

Key Definitions

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

Comparative Analyses Outcomes

- For each physical, task, or labeling comparison performed during CA, provide one of the following outcomes:
  - **No Differences**
  - **Minor Design Difference**
    - If the difference in the user interface of the proposed generic combination product, in comparison to the user interface of the RLD do not affect an external critical design attribute
  - **Other Design Difference**
    - If any aspect of the comparative analyses suggests that difference in the design of the user interface of a proposed combination product as compared to the RLD *may* impact an external critical design attribute -that involves administration of the product
- Consider any identified differences in the context of the overall risk profile of the product

Comparative Analyses: Best Practices

- Identify ALL user interface differences
- Classify ALL differences based on definitions in the guidance
- Focus on potential differences in the critical tasks between the RLD and proposed generic drug-device combination products.
  - Remember that **not every task is a critical task**
- Consider the product and its context of use
  - Same difference could be classified and assessed differently
  - Focus on individual RLD

Best practice: Always consider context of use

Context of use

- **Urgency of use**: Emergency vs. non-emergency
- **Frequency of use**: Single use vs. repeated use
- **End-users**: Patients, caregivers, healthcare professionals
- **Environment of use**:
  - Clinical: hospital, clinic
  - Nonclinical: home, school, etc.
- **Patient population**:
  - Dexterity issues (rheumatologic, neuromuscular disorder)
  - Incapacitated (naloxone HCl)

Evaluating Other Design Differences

Critical Tasks & Critical Design Attributes

A brief review…

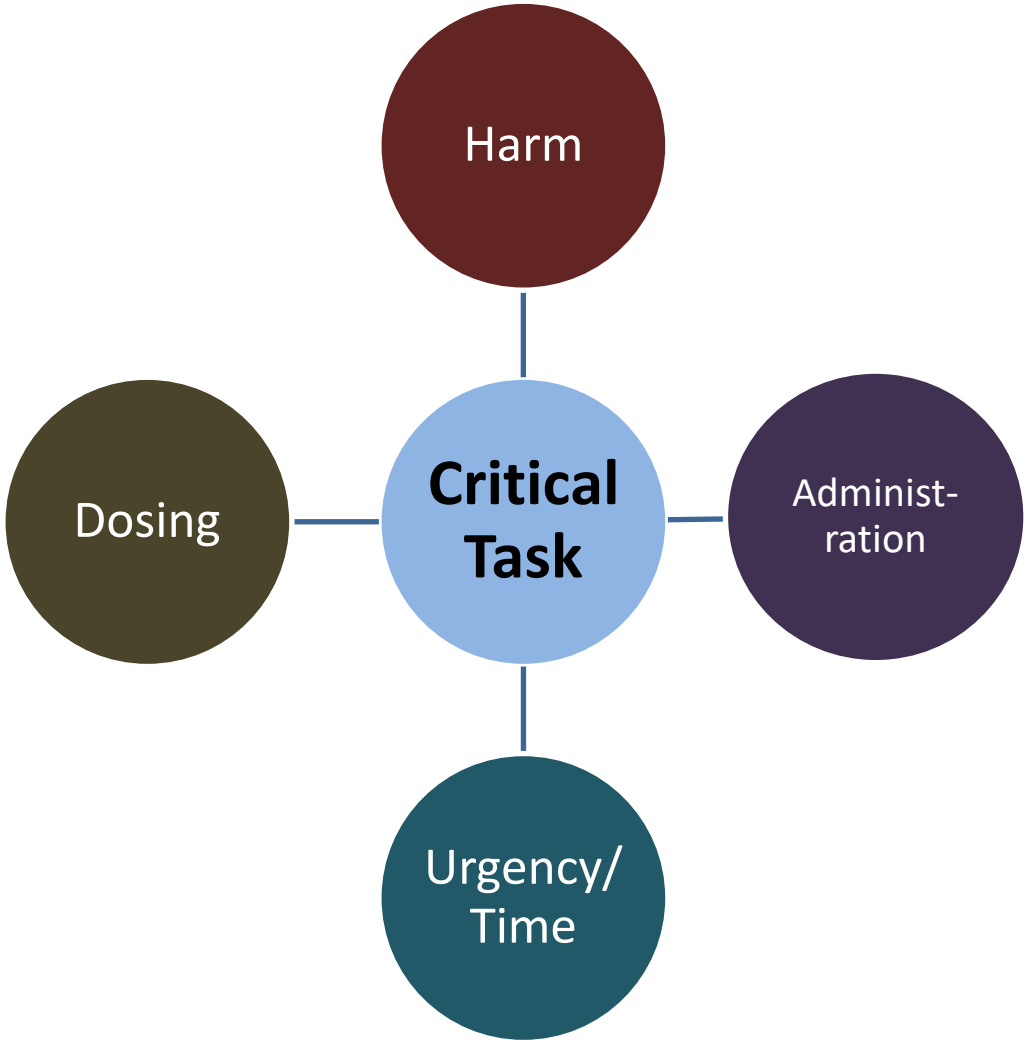
- **Critical task:** A user task that, if performed incorrectly or not performed at all, would or could cause harm to the patient or user, where harm is defined to include compromised care
- **External critical design attribute:** Those features that directly affect how users perform a critical task…the external critical design attributes of the product would be those features that end-users rely on to safely and effectively perform…critical tasks

Does this mean…every task that could result in a medication error is a critical task?...

and, therefore, that all differences are other design differences?

NO

Then what should a potential applicant consider when identifying a critical task?



Yikes!…I have an “other” difference!

It is not time to panic.

www.fda.gov

If I have **other design differences** between the user interfaces of the RLD and my generic, do I have to conduct a **CUHF study**?

No! Not necessarily!

When there are other design differences…

What are my options?

- When CA identify other design differences, consider:
  - **Re-design** of the proposed generic user interface to minimize differences from the RLD
  - **Potential need for additional information and/or data** to support the ANDA submission
    - You may already have the information or data that FDA needs!

What Else Can I Do?

- **Work through the following scenario:**

  What happens if a user engages the other design difference inappropriately?

  - What is the risk if the anticipated error occurs?
  - Does it impact your proposed generic having the *same clinical effect and safety profile* as the RLD*?*
  - Why or why not?
  - What can you do to address this?

  [answers are affected by drug product profile, intended users and use environments]

Example 1: Dry Powder Inhaler

- Product-Specific Guidance for Fluticasone Propionate/ Salmeterol Xinafoate (FP/SX) posted in September 2013
- Recommendation include studies for bioequivalence, formulation sameness and device considerations
- First Generic FP/SX DPI approved in January 2019
- Device and user interface considerations
- Other differences addressed with additional data appropriate for submission in ANDA

RLD and Generic FP/SX DPI

Figure A

https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/021077s061lbl.pdf

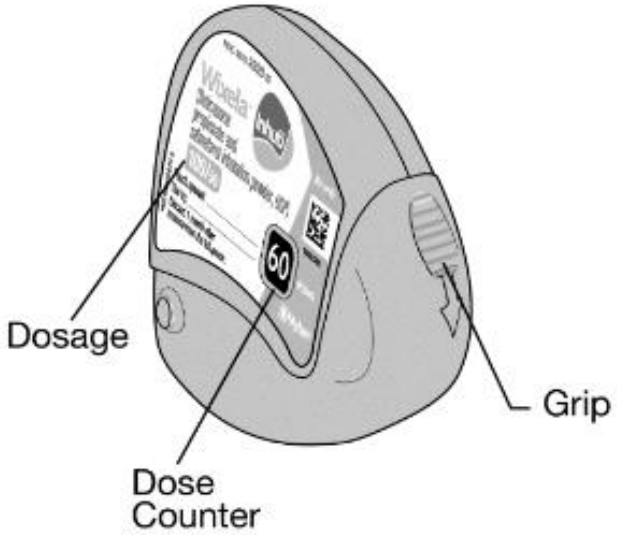
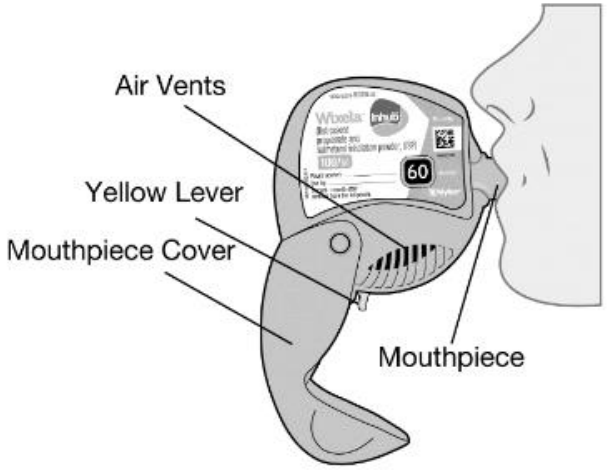


Figure A

https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/208891Orig1s000lbl.pdf

RLD (left) & Generic (right) FP/SX DPIs

Inhale your medicine



Close the device

- **Potential use error:** Following generic substitution, user could hold generic DPI in the horizontal plane orientation (like the RLD) rather than the intended vertical plane orientation.
- **Potential harm:** This might alter the drug dose reaching the distal airways and alter overall efficacy and safety profile of generic compared to RLD.
- **Solution:** Applicant submitted data demonstrating that if users made this error, it did not affect drug deposition pattern.

https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/021077s061lbl.pdf

https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/208891Orig1s000lbl.pdf

Example 2: Vial (RLD) to Prefilled Syringe

- Other design difference
- When is this an “acceptable” other design difference?
- When is additional information or data needed to support this difference in presentation?
- Considerations:
  - What is the context of use (environment of use, intended users, labeled indications, and dosing etc.)
  - What is the risk if the errors occur?

Example 2: Vial (RLD) to Prefilled Syringe (cont.)

- May be acceptable differences in user interface…without additional support from CUHF study data
- **Factors that may impact this decision:**
  - Are there critical tasks that have been removed?
  - Are new critical tasks introduced?
    - For example, would drug need to be expelled from the PFS to achieve the correct dose?
  - Has the PFS been designed to support all labeled dosing? (e.g., correct syringe markings).

Comparative Analyses Challenge:

Best Practices when the RLD is Unavailable

Unavailable RLD…Comparative Analyses?

- Compare the proposed user interface of the generic drug-device combination product to the user interface of the **RLD**
- When the RLD is discontinued and samples are unavailable, performing the comparison to the **RLD** is more challenging but still required.
- How can you conduct complete CA without the RLD?

CA Challenges When RLD is Unavailable

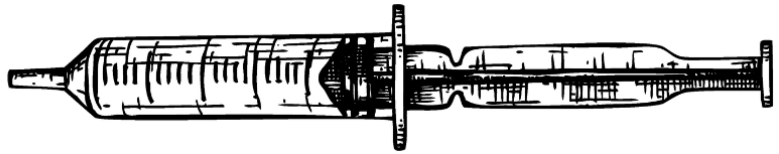
- Labeling Comparison
  - RLD discontinued many years ago; never had IFU
- Physical Comparison
  - Discontinued, no samples available
- Comparative Task Analysis
  - Proposed container closure is different than RLD
  - No Instructions for Use (IFU) describing step-wise use process; no samples for hands-on experience

Labeling Comparison

- Labeling comparison should focus on the IFU and labeling sections related to user interface.
- Use most recent version of RLD labeling
  - Drugs@FDA
  - If RLD labeling cannot be found in the public domain, consider submitting a CC asking about next steps
  - All approved RLD labeling is available through FDA's Division of Freedom of Information

Physical Comparison

- Information from labeling
  - Images or sketches
  - Physical descriptions
- Documents that supported RLD approval
  - Some may be available online with some redactions (see Drugs@FDA and try Google search)
- Promotional Materials from RLD Sponsor*
- General knowledge of common container closures



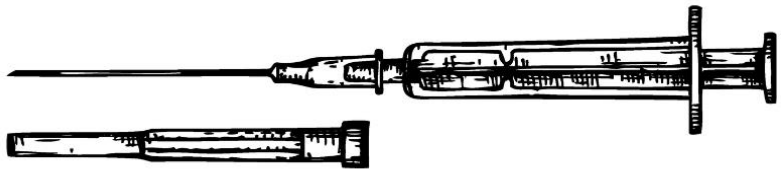
*must be for the FDA approved product

Comparative Task Analysis

- Most tasks can be determined from:
  - Overall container closure
    - E.g., general knowledge of correct use of a glass vial, oral dosing cup, or syringe
  - Additional details of container closure description in the RLD labeling
    - E.g., presence of a dust cap
- If the proposed container closure is different from the RLD, tasks described should reflect those differences.

Supportive Information

- The **primary comparison** must be conducted between the proposed generic product and its **RLD**; however…
- Currently marketed products may be used as supportive information
  - E.g., RLD was a single dose glass vial, proposed and all other approved and marketed products are single dose prefilled syringes



We look forward to your questions during the panel discussion.