Product Development and Human Factors Considerations:
Navigating the Halls of FDA/CDER

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I plan to develop a combination product under an NDA or BLA, who in the Center for Drug Evaluation and Research (CDER) will I primarily interact with regarding my Human Factors (HF) development program?
Office of New Drugs (OND)

- What they do:
  - Provide regulatory oversight for investigational studies during drug development
  - Make decisions regarding marketing approval for new (innovator or non-generic) drugs, including decisions related to changes to already marketed products
  - Provide guidance to regulated industry on a wide variety of clinical, scientific, and regulatory matters
- Therapeutic Biologics and Biosimilars Staff (TBBS) is housed in the immediate office of the OND
- Organized by therapeutic area
- OND Division will be your primary point of contact for most HF submissions submitted under 505(b)(1), 505 (b)(2), 351(a), 351(k), and 351(k)(4) regulatory pathways
Office of Medical Policy (OMP)

• What they do:
  – Provide scientific and regulatory leadership in the development of medical policy
• The Division of Medical Policy Programs (DMPP) – Patient Labeling Team is housed within OMP
  – OND and OGD consult DMEPA for human factors (HF) protocol submissions
  – DMEPA consults Patient Labeling Team (PLT) in the Office of Medical Policy for the review of Instructions for Use (IFU) and/or Quick Reference Guides for laypersons that are submitted with human factors protocols
  – DMEPA incorporates PLT recommendations into review of HF protocols
Office of Surveillance and Epidemiology (OSE)

• What they do:
  – Maintains a system of postmarketing surveillance and risk assessment programs to identify adverse events that did not appear during the drug development process
  – Learns about and evaluates adverse events submitted to FDA’s MedWatch program, which totals more than 1.6 million reports per year
  – Identify drug safety concerns and recommend actions to improve product safety and protect the public health

• The Division of Medication Error Prevention and Analysis (DMEPA) is housed within OSE
Division of Medication Error Prevention and Analysis (DMEPA)

• Created in 1999
• Scientists and healthcare professionals with varied backgrounds
• 56 FTEs
• Aligned by therapeutic areas
• Leads CDER review pertaining to medication error prevention and analysis and human factors for drugs and therapeutic biologics
DMEPA Mission

To increase the **safe use** of drug products by minimizing use error that is related to the *naming, labeling, packaging, or design* of drug products
Proprietary Names

Guidance/Work Groups/AC/etc.

DMEPA

Postmarket Surveillance/Signals

Human Factors

Labels/Labeling/Packaging/Product Design
Human Factors (HF) Evaluation in CDER

DMEPA is the lead for review of HF submissions (e.g., protocols, study reports, etc.) within CDER

- Evaluates HF submissions for drugs, biologics, and combination products regulated by CDER
- DMEPA will identify the need for and issue inter-center consults to the CDRH Human Factors Team as needed
For NDAs and BLAs, what are timelines that I need to be aware of for my human factors development program?
# Drug Development Process

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Preclinical Testing</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
<th>Phase 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Purpose</td>
<td>Laboratory and animal studies</td>
<td>20-100 healthy volunteers</td>
<td>100s patient volunteers</td>
<td>1,000s patient volunteers</td>
<td>General population</td>
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- **Preclinical Testing**
  - **Purpose**: Gather basic information on safety and efficacy of product.
  - **Subjects**: Laboratory and animal studies.

- **Phase 1**
  - **Emphasis on safety**. Goal is to determine product’s most frequent side effects and often, how drug is metabolized and excreted.
  - **Subjects**: 20-100 healthy volunteers.

- **Phase 2**
  - **Emphasis on effectiveness**. Goal is to determine whether the drug works in indicated patient population. Continue safety evaluation and short-time side effects.
  - **Subjects**: 100s patient volunteers.

- **Phase 3**
  - Gather more information on safety and effectiveness, study different populations, different dosages, and use of drug in combination with other drugs.
  - **Subjects**: 1,000s patient volunteers.

- **Phase 4**
  - Postmarket monitoring stage after drug gets on the market.
  - **Subjects**: General population.

**FILE IND**

**FILE NDA/BLA**
## Drug Development Process & Human Factors Considerations for Commercial (to-be-marketed) Product

<table>
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<tr>
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<tbody>
<tr>
<td>FILE IND</td>
<td></td>
<td></td>
<td>FILE NDA/BLA for FDA review</td>
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***DMEPA involvement (can be as early as pre-IND phase)***

Human factors (HF) product design, preliminary analyses, formative work, and HF validation testing
CDER 21st Century Review Process

- **Application Day 0**
- **Filing/Planning Meetings Day 45** (Day 30 for Priority)
- **Mid-Cycle Meeting Month 5** (3 for Priority)
- **Wrap Up Meeting Month 8** (5 for Priority)
- **Action Date Month 10** (6 for Priority)

**1. Pre Submission Activities**
**2. Process Submission**
**3. Plan Review**
**4. Conduct Review**
**5. Take Official Action**
**6. Post Action Feedback**

**Note:** The timeline for review of NMEs/BLAs under PDUFA V’s “Program” Review extends the Conduct Review Phase by two months.
CDER 21st Century Review Process: NMEs* & Original BLAs under PDUFA V

*New Molecular Entity (NME): an active ingredient that has never before been marketed in the United States in any form.
Current Timelines for DMEPA Review

• DMEPA strives to review submissions in a timely manner:
  – Review of use-related risk analysis (URRA) in 60 days
  – Review of human factors protocol in 90 days
  – Review of human factors study report during the application submission
What are some key things I need to know about meeting with FDA/CDER regarding HF for my NDA or BLA?
Meet with FDA/CDER Early in Development

• Why meet with FDA/CDER?
  – To ensure that both the Sponsor and the Agency are in alignment with the development programs for the drugs/therapeutic biologics and combination products
  – To obtain Agency’s feedback on the product’s HF development programs
Meeting Types*

• Type A
  – Necessary for an otherwise stalled product development program to proceed or to address an important safety issue
  – Example: after an FDA regulatory action other than approval (e.g., issuance of a complete response letter)

• Type B
  – Includes Pre-IND meetings, End-of-phase 2/pre-phase 3 meetings, Pre-NDA meetings, Pre-BLA meetings, etc.

• Type C
  – Any meeting other than Type A or Type B regarding the development and review of a product
  – Can request a written response to questions rather than face-to-face meetings

• See Guidance for Industry: Formal Meetings Between the FDA and Sponsors or Applicants for more information

*Applies to meetings associated with new drug applications or biologics license applications (BLAs) under section 351(a) of the PHS Act
Meeting Types*

- **Biosimilar Initial Advisory Meeting**
  - Initial assessment limited to a general discussion regarding whether licensure under section 351(k) of the PHS Act may be feasible for a particular product, and, if so, general advice on the expected content of the development program

- **BPD Type 1 Meeting**
  - Necessary for an otherwise stalled BPD program to proceed

- **BPD Type 2 Meeting**
  - Discuss a specific issue (e.g., proposed study design or endpoints) or questions where the FDA will provide targeted advice regarding an ongoing BPD program
  - Can include substantive review of summary data, but does not include review of full study reports

- **BPD Type 3 Meetings**
  - In-depth data review and advice meeting regarding an ongoing BPD program

- **See Guidance for Industry: Formal Meetings Between the FDA and Biosimilar Biological Product Sponsors or Applicants**

*Applies to biosimilar biological products intended to be submitted under 351(k) of the Public Health Service Act (PHS Act)
Pre-NDA/Pre-BLA/BPD-Type 4 Meetings

• Purpose is to discuss format and content of anticipated application
  – Reviewers also describe how data should be presented in the NDA/BLA to facilitate its review

• At pre-NDA/BLA meetings:
  – FDA and the applicant will agree on the content of a complete application for the proposed indication(s), including preliminary discussions on the need for Risk Evaluation and Mitigation Strategies (REMS) or other risk management actions.

• Format/contents for submission of HF data* will also be discussed at this time

* If determined necessary during the IND phase
In addition to post mid-cycle communication and the late-cycle meeting with Applicants (required for PDUFA V “Program”), applicants or the review team can request a meeting at any time during the review process.
HF Questions in Meeting Packages

• Meetings should **NOT** be used to obtain Agency review of HF study protocols or result reports

• Meeting packages can include specific questions regarding plans and timeline for HF development program
What are some key points that CDER expects me to understand regarding my human factors development program for my NDA or BLA?
HF is Not Just a Checkbox At the End of Development

You are applying human factors engineering (HFE) to your entire product development process.
HF Can Help Minimize Use Error Error

- **Optimized design**
- **Original design**
- **Reduce risk through Human Factors**

**Risk Level**
- **Low risk product**
- **High risk product**

[www.fda.gov](http://www.fda.gov)
We Have a Mutual Goal

• From a human factors perspective, the **mutual goal** between FDA and Industry is to market a product with a user interface* that supports safe and effective use
  – Ensure best utilization of FDA and Industry resources
  – Allow for open communication and collaboration between FDA and Industry

*User interface: includes all points of interaction between the product and the user(s) including elements such as displays, controls, packaging, product labels, instructions for use, etc.
Your User Interface (UI)* is Not Just the Device

User interface: includes all points of interaction between the product and the user(s) including elements such as displays, controls, packaging, product labels, instructions for use, etc.

E.g.,
- Labeling
- Packaging
- Delivery device constituent part, and any associated controls and displays

*Draft Guidance for Industry: Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA
We Look at the Entire Product

Device

Drug/Biologic

Combination Products

What are additional considerations for combination products?
We Want You to Come to Us Early

Collaborate with CDER in the early development of any proposed combination product! Send us your questions earlier rather than later.
We’d Like to Review Your Protocol

Protocols should generally be submitted separately to the IND (do not include as part of a meeting package)

*See PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2018 Through 2022
What are some documentation expectations that I should be aware of for my HF submission?
356(h) and 1571 Forms

• A submission that is the subject of an active IND should include FDA Form 1571 (Investigational New Drug Application (IND))
• A submission that is the subject of a marketing application should include FDA Form 356h (Application to Market a New or Abbreviated New Drug or Biologic for Human Use)
• Refer to the [FDA Forms website](http://www.fda.gov/aboutfda/reportsmanualsforms/forms/default.htm)* for the latest versions of these forms and their corresponding instruction files

*See FDA Forms website [http://www.fda.gov/aboutfda/reportsmanualsforms/forms/default.htm](http://www.fda.gov/aboutfda/reportsmanualsforms/forms/default.htm)
If the submission contains Human Factors (HF) information, select ‘Yes.’ HF information may include a study protocol, results report, use-related risk analysis, or justification for no HF validation study.
Update to 1571 Form

Check “other” if you have a use-related risk analysis, HF results report, etc.

Check here if you have a protocol for a HF validation study
PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2018 Through 2022 (AKA PDUFA VI) Considerations
PDUFA VI Considerations

I. Enhancing Regulatory Science and Expediting Drug Development

• 5.e. FDA will establish submission procedures for Human Factors protocols no later than September 30, 2018. Beginning in FY 2019, FDA will establish timelines to review and provide comment on the protocols for Human Factors studies of combination drug-device and biologic-device products within 60 days.

  – (2) Within 60 days of Agency receipt of the protocol and specific questions, the Agency will provide a written response to the sponsor that includes a succinct assessment of the protocol and answers to the questions posed by the sponsor. If the Agency does not agree that the protocol design, execution plans, and data analyses are adequate to achieve the goals of the sponsor, the reasons for the disagreement will be explained in the response.

PDUFA VI Considerations

• Performance goals for FDA will be phased in, starting in FY 2019:
  – By FY 2019, review 50% of human factors protocol submissions within 60 days and provide sponsor with written comments.
  – By FY 2020, review 70% of human factors protocol submissions within 60 days and provide sponsor with written comments.
  – By FY 2021, review 90% of human factors protocol submissions within 60 days and provide sponsor with written comments.
Procedural Guidance

• Pending Draft Guidance: Contents of Threshold Analyses and Human Factors Submissions to an NDA, BLA or ANDA

PDUFA VI Considerations

I. Enhancing Regulatory Science and Expediting Drug Development

• 5.c. FDA will establish Manuals of Policies and Procedures (MAPPs) and Standard Operating Policy and Procedures (SOPPs) to promote efficient, effective, and consistent combination product development and review. The documents will describe processes and procedures for conducting review of combination products, including the expectations for consultation of internal experts outside the reviewing Center. FDA will describe the responsibilities of staff in each Center and Office, expectations for core review team members and for other consultant staff in activities and meetings related to the combination product development program and application review. FDA will define the key terms to be used by staff in review of combination products to foster clear communication within FDA and to regulated industry. The topic areas and expected completion dates of these documents are specified below:

  i. Human Factors Assessments (March 31, 2019)

  iii. Patient-oriented labeling, including instructions-for-use materials for those drug-device and biologic-device combination products regulated by CBER and CDER (September 30, 2019)
PDUFA VI Considerations

5.h. By the end of FY 2019, FDA will publish draft guidance or update previously published guidance issued by the medical product centers and OCP for review staff and industry describing considerations related to drug-device and biologic-device combination product on the topics noted below. The draft guidance(s) will be finalized by the end of FY 2022.

i. Bridging studies, including the bridging of data from combination products that employ different device components for the same drug or biologic and the same device component across different drugs and biologics.
What is the Regulatory Question?

- Is there adequate data to support that the intend-to-market product is safe and effective?
  - What was evaluated in clinical trials vs. what does the sponsor intend to market?
    - If there are differences, is additional data warranted to bridge the two?

This question is not a new question
What is the Regulatory Question?

Example Clinical Question
• Can patients tolerate repeated self-injection with this autoinjector presentation for this viscous drug product? What is the local adverse event profile over time?

Example HF Question
• Can patients hold the button for the required 20 seconds associated with the task of injection?
Questions for Sponsors

1. How do sponsors interpret the language on patient handling studies in the Draft Guidance for Industry *Rheumatoid Arthritis: Developing Drug Products for Treatment*?

2. What process do sponsors currently follow to evaluate the relevance of data that already exists in your databases when a change in presentation or formulation is pursued? How do you then identify the need for bridging data and/or new clinical data to establish safety/effectiveness of the final combination product?

3. What changes do sponsors think can be supported by non-clinical bridging data vs. what changes will require new clinical studies? Please provide examples.

4. What data do sponsors think are warranted in order to bridge different presentations or formulations?
   - Does it depend on the difference? If yes, how so?

5. How does industry determine what type of data are needed to establish device constituent part robustness is maintained when device changes are implemented?

6. What guidance do sponsors want when it comes to bridging data considerations?
Are there additional resources I should be aware of?
# HF Guidances Are Available

<table>
<thead>
<tr>
<th>Regulatory Pathway(s)</th>
<th>New Drug</th>
<th>Generic</th>
<th>Biosimilar</th>
<th>Interchangeable</th>
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<tr>
<td>505(b)(1), 505(b)(2), 351(a)</td>
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<td>NDAs, and BLAs</td>
<td>ANDAs</td>
<td>BLAs</td>
<td>BLAs</td>
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<tr>
<td>Released February 2016</td>
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Additional Information

• Guidance for Industry and FDA Staff – Applying Human Factors and Usability Engineering to Optimize Medical Device Design; http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm259748.htm


Questions

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