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

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Center for Drug Evaluation and Research (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)

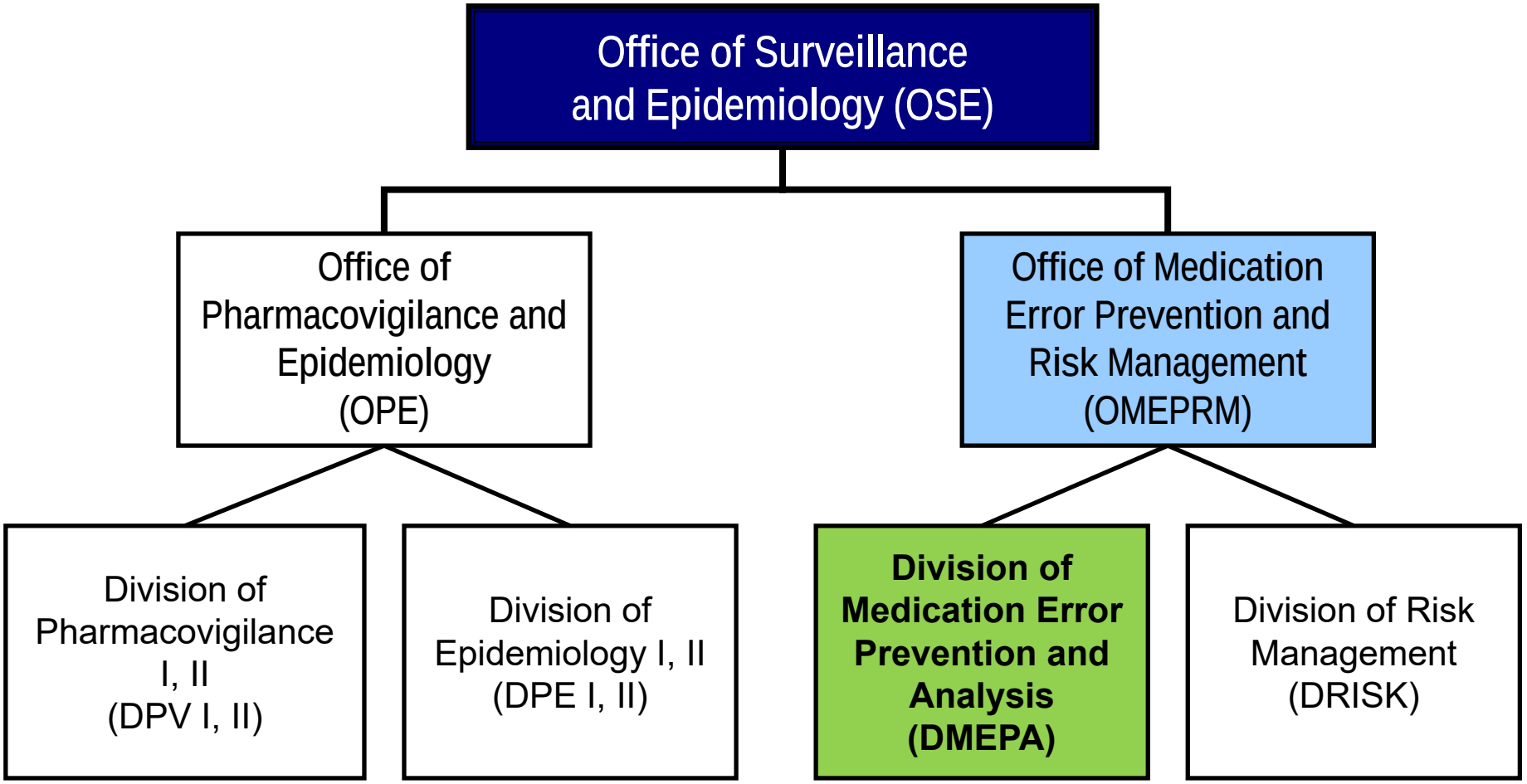
- What they do:
  - Provide regulatory oversight for investigational studies during drug development
  - Make decisions regarding marketing approval for new (innovator or non-generic) drugs, including decisions related to changes to already marketed products
  - Provide guidance to regulated industry 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

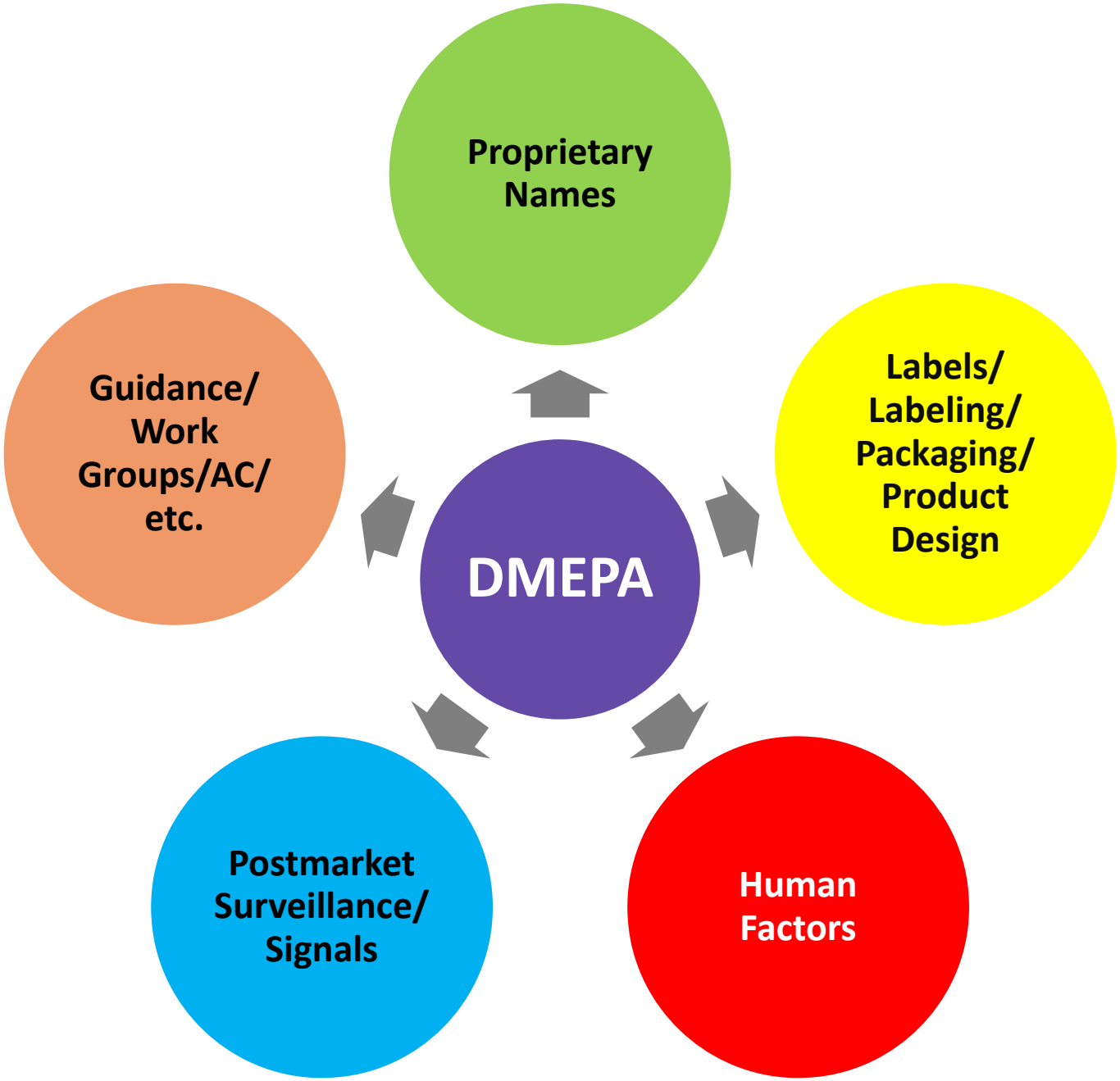

Office of Surveillance and Epidemiology (OSE)
Office of Pharmacovigilance and Epidemiology (OPE)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Division of Pharmacovigilance I, II (DPV I, II)
Division of Epidemiology I, II (DPE I, II)
Division of Medication Error Prevention and Analysis (DMEPA)
Division of Risk Management (DRISK)

Division of Medication Error Prevention and Analysis (DMEPA)

- Created in 1999
- Scientists and healthcare professionals with varied backgrounds
- 51 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
Labels/ Labeling/ Packaging/ Product Design
Human Factors
Postmarket Surveillance/ Signals
Guidance/ Work Groups/AC/ etc.
DMEPA

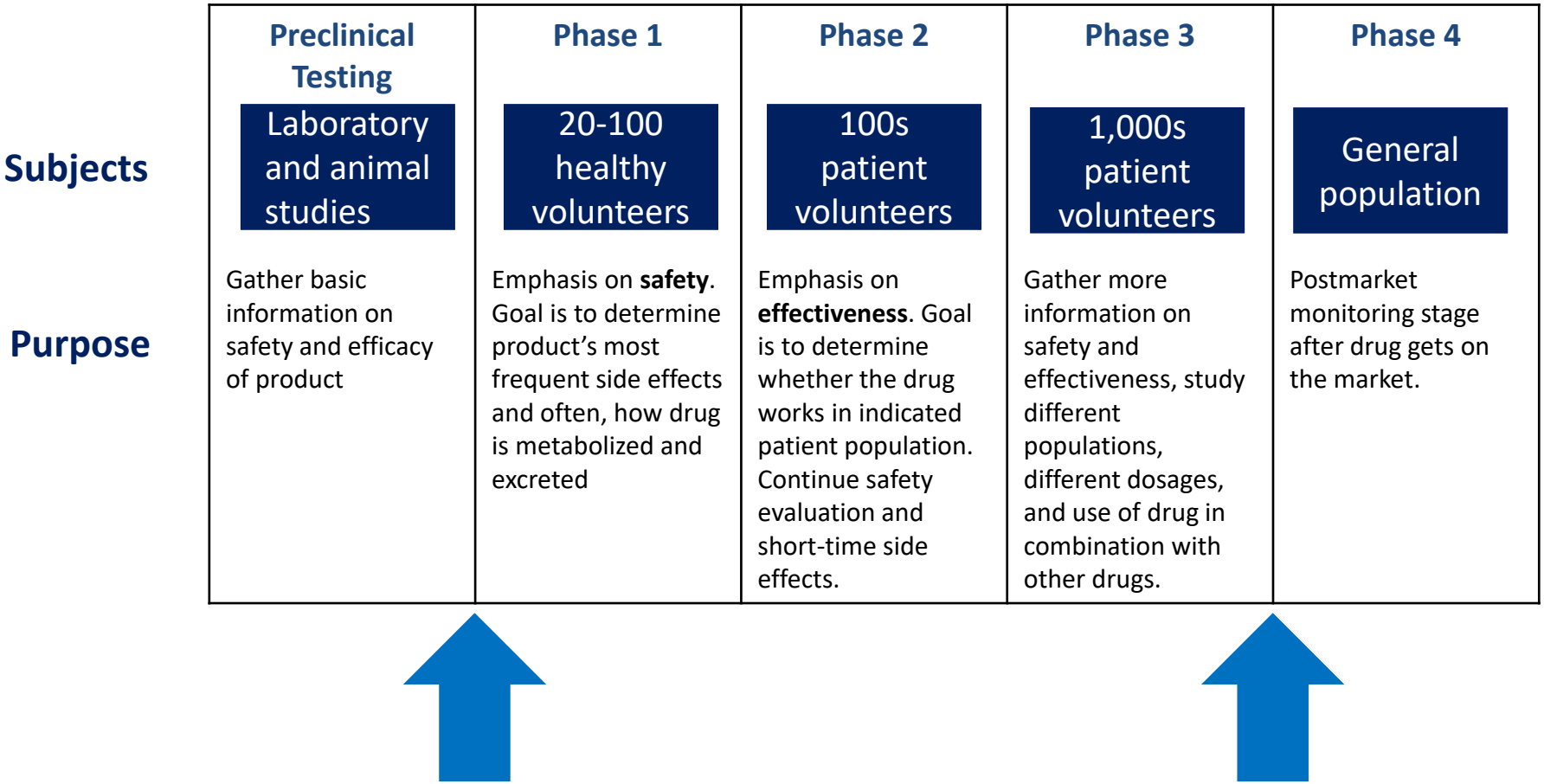
Human Factors (HF) Evaluation in CDER

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

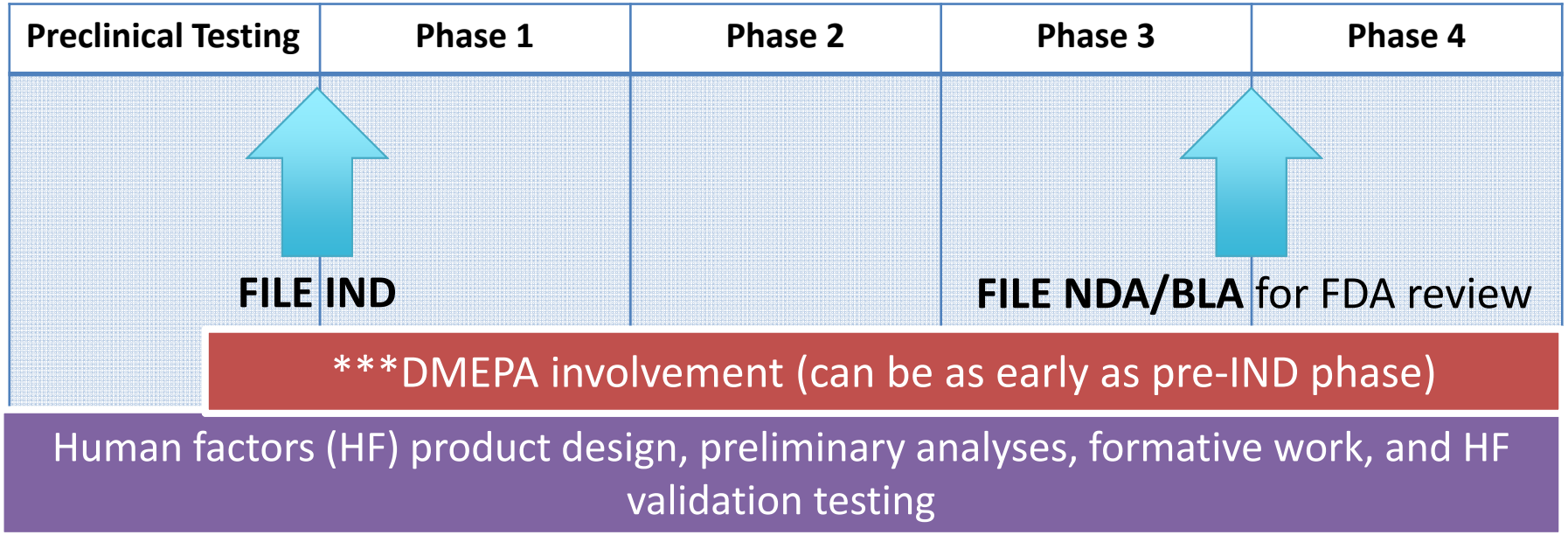
- Evaluates HF submissions for drugs, biologics, and combination products regulated by CDER
- DMEPA will identify the need for and issue inter-center consults to the CDRH Human Factors Team as needed

For NDAs and BLAs, what are timelines that I need to be aware of for my human factors development program?

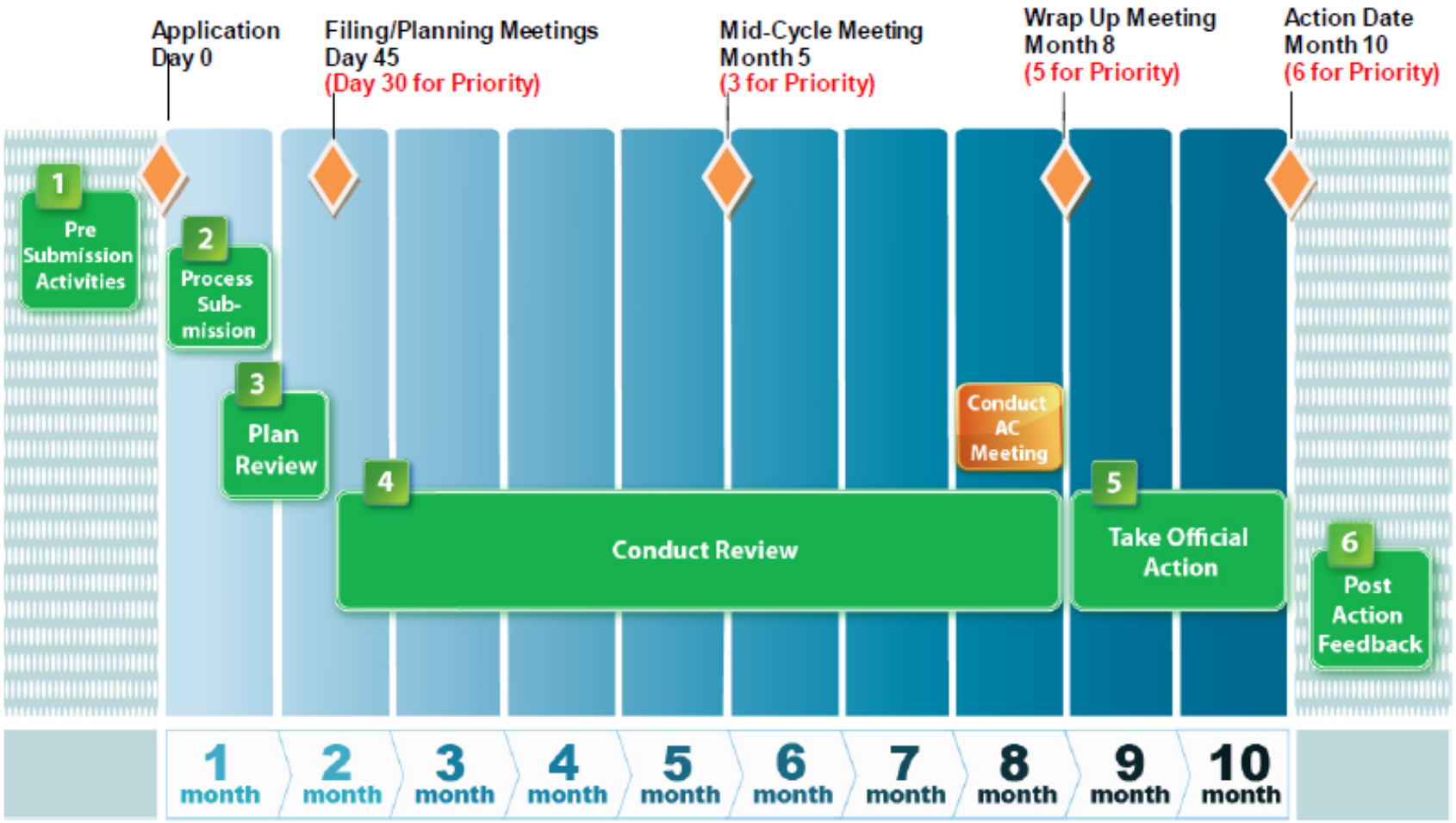
Drug Development Process



Drug Development Process & Human Factors Considerations for Commercial (to-be-marketed) Product

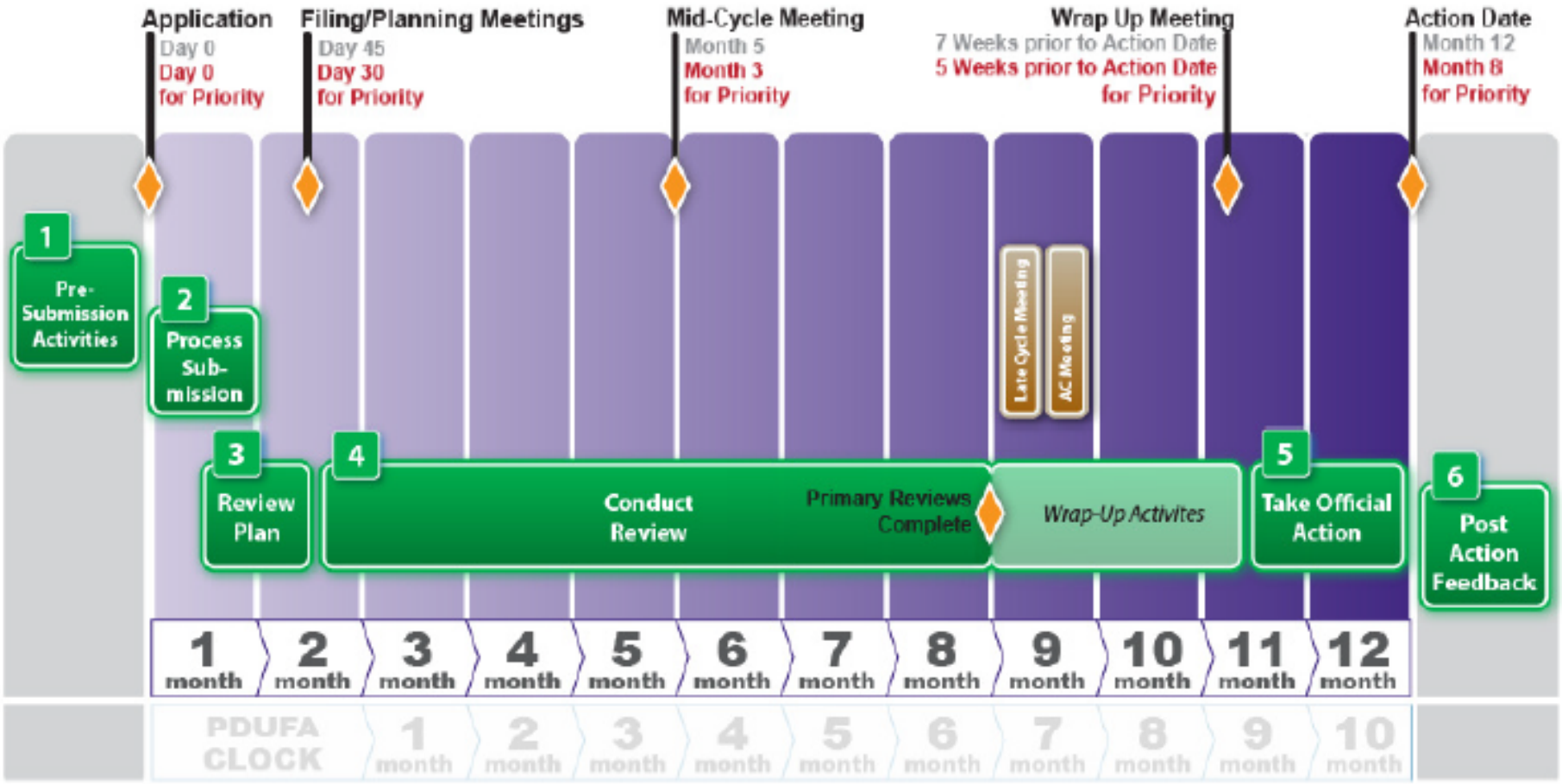


CDER 21st Century Review Process



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)

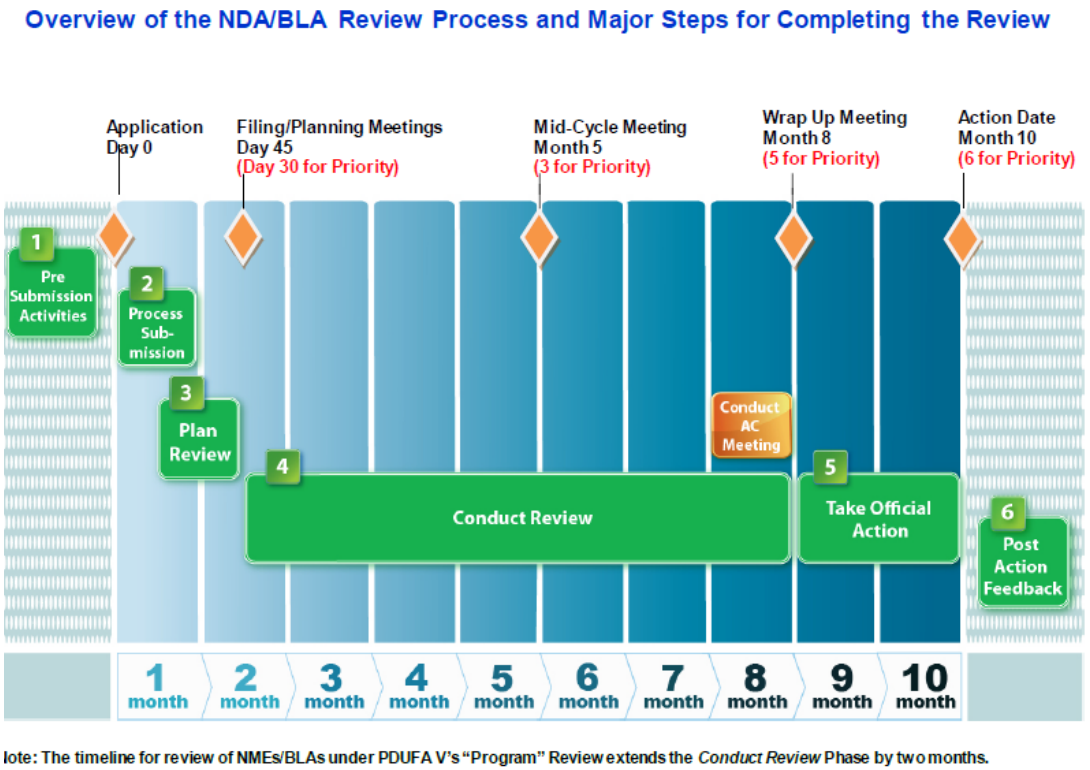
Pre-NDA/Pre-BLA/BPD-Type 4 Meetings

- 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

CDER 21st Century Review Process

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

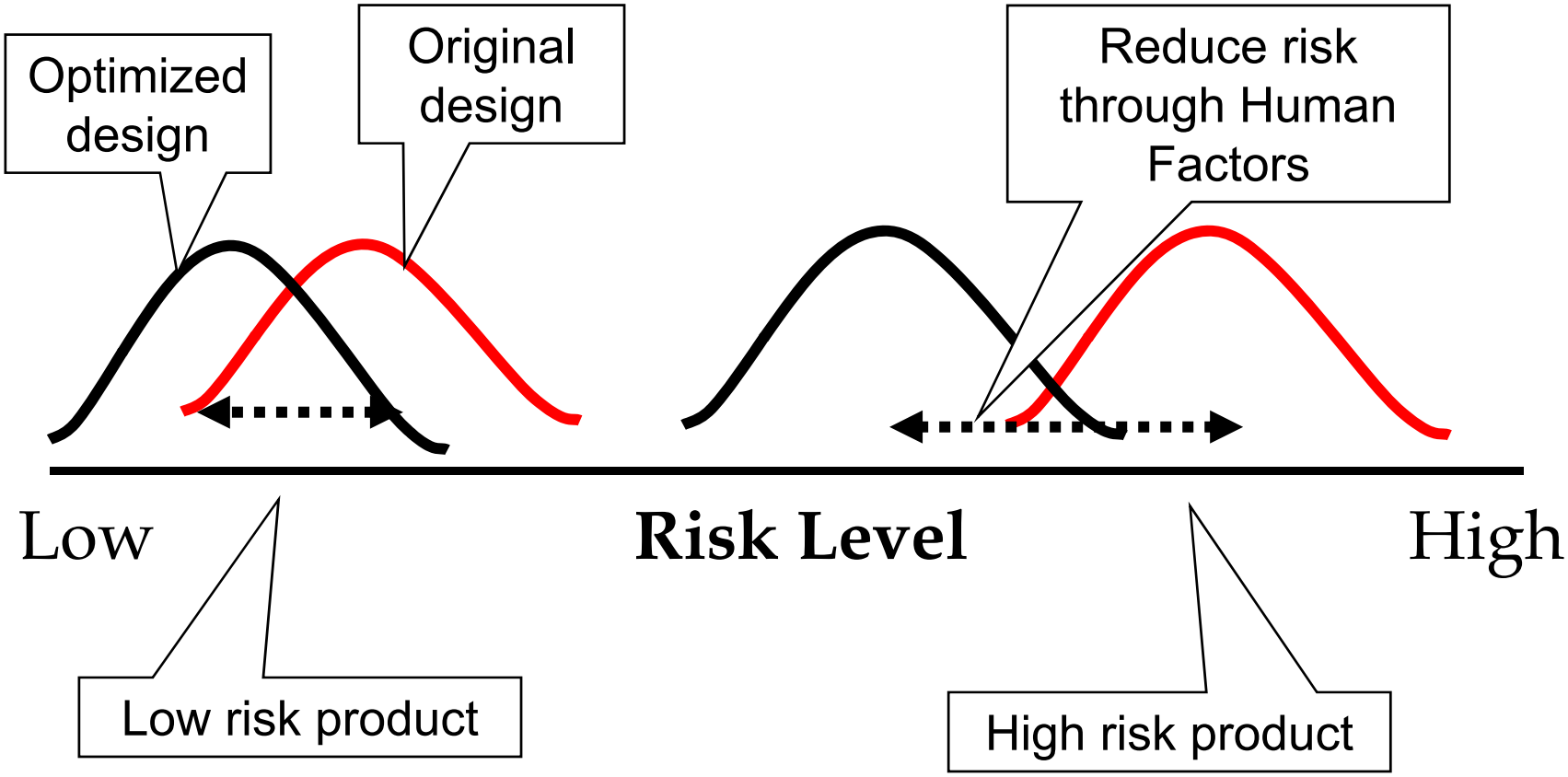
- Meetings should **NOT** be used to obtain Agency review of HF study protocols or result reports
- Meeting packages can include specific questions regarding plans and timeline for HF development program

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



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

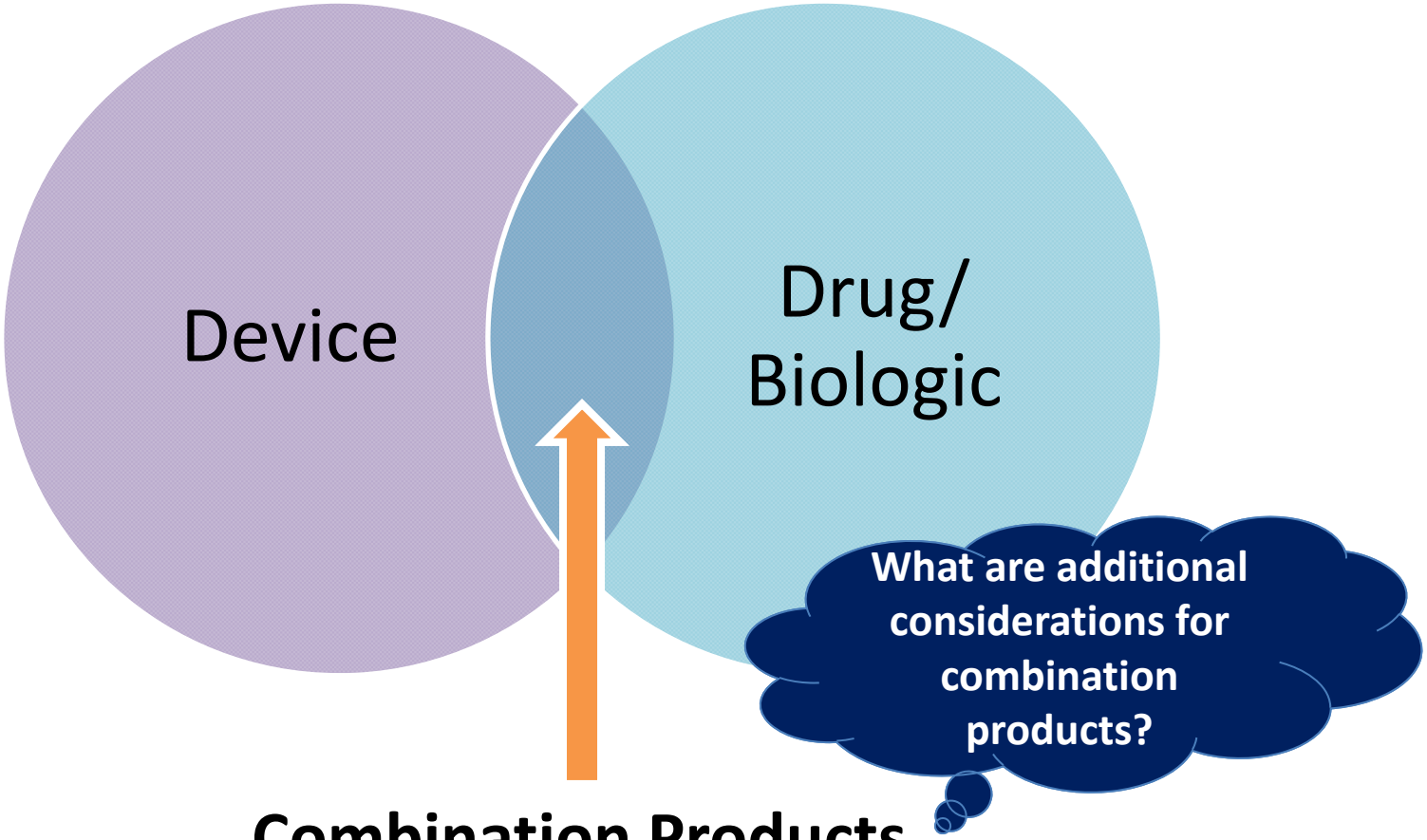
User interface: includes all points of interaction between the product and the user(s) including elements such as displays, controls, packaging, product labels, instructions for use, etc.

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



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

- CDER currently requests 90 days for review of standard HF validation protocols
- Beginning in FY 2019, FDA will establish timelines to review and provide comment on the protocols for HF studies of combination drug-device and biologic-device products within 60 days*
- 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

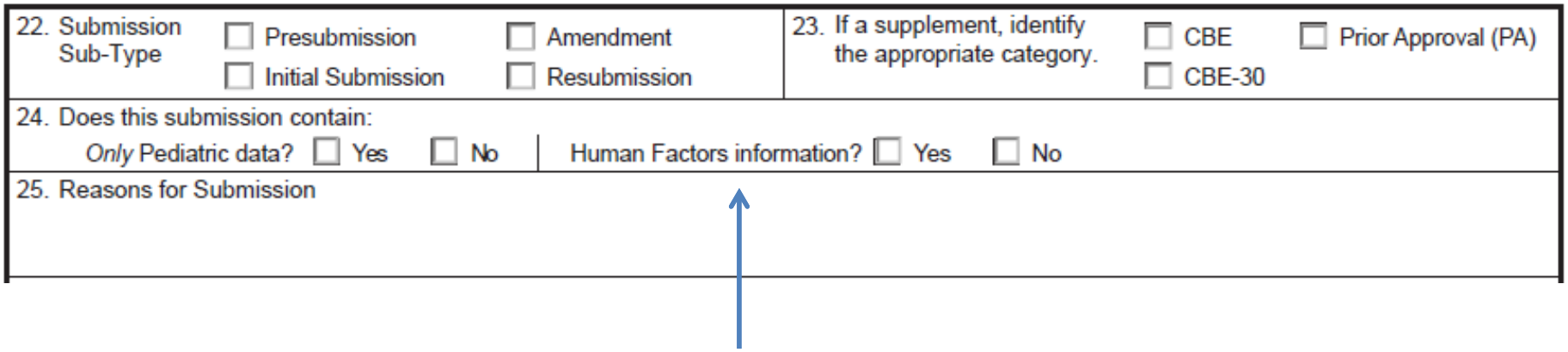
What are some documentation expectations that I should be aware of for my HF submission?

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* 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

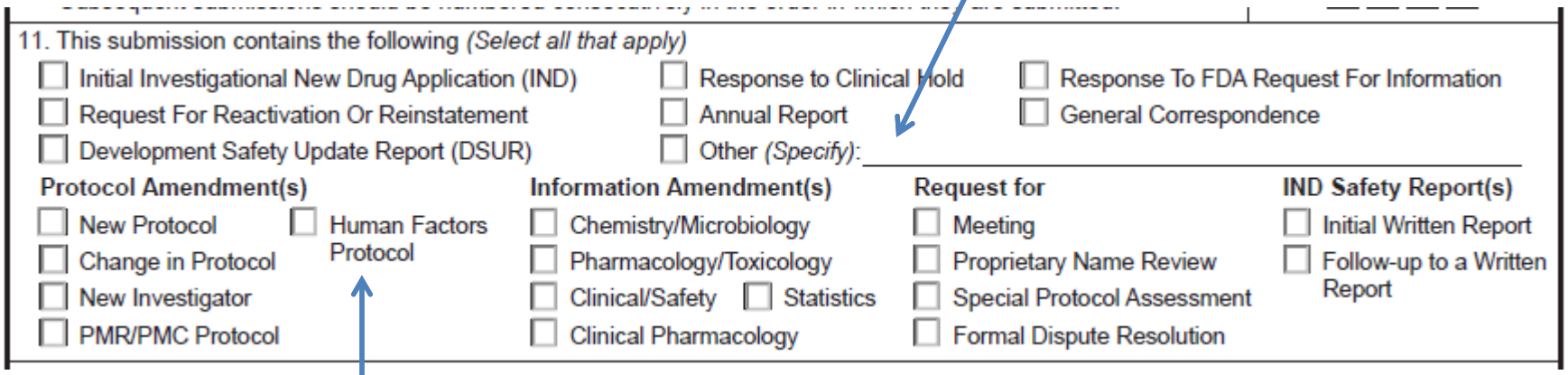
Update to 356h Form



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.



11. This submission contains the following *(Select all that apply)*

- ☐ Initial Investigational New Drug Application (IND)
- ☐ Request For Reactivation Or Reinstatement
- ☐ Development Safety Update Report (DSUR)
- ☐ Response to Clinical Hold
- ☐ Annual Report
- ☐ Other *(Specify)*: _____
- ☐ Response To FDA Request For Information
- ☐ General Correspondence

Protocol Amendment(s)

- ☐ New Protocol
- ☐ Change in Protocol
- ☐ New Investigator
- ☐ PMR/PMC Protocol
- ☐ Human Factors Protocol

Information Amendment(s)

- ☐ Chemistry/Microbiology
- ☐ Pharmacology/Toxicology
- ☐ Clinical/Safety
- ☐ Statistics
- ☐ Clinical Pharmacology

Request for

- ☐ Meeting
- ☐ Proprietary Name Review
- ☐ Special Protocol Assessment
- ☐ Formal Dispute Resolution

IND Safety Report(s)

- ☐ Initial Written Report
- ☐ Follow-up to a Written Report

Check here if you have a protocol for a HF validation study

HF Validation Study Protocol Submission

- Background information
  - Who are the intended users and use environments?
  - What will the interface consist of?
  - What are known use problems with previous or similar products?
  - What did you learn and see during your preliminary analyses and formative evaluations?

HF Validation Study Protocol Submission

- Analysis of hazards and risks associated with use of the product
  - Use-related risk analysis should be based on task analysis
    - What harm can result from each use error?
    - What measures did you take to reduce risk?
    - How will you measure effectiveness of measures you took?

HF Validation Study Protocol Submission

- Testing Details
  - What's your study objective?
  - Will your study be simulated or actual-use?
  - What will the test environment(s) be?
  - What are the details of training, if applicable?
  - What are the user groups?
  - What user tasks and knowledge tasks will be included?

HF Validation Study Protocol Submission

- Testing Details Cont'd
  - How do you define success or failure of task performance?
  - How will you collect data?
  - How will you perform your root cause analysis?
  - Is there leading language in your moderator transcript?
- Product samples are helpful

Are there additional resources I should be aware of?

HF Guidances Are Available

	New Drug	Generic	Biosimilar	Interchangeable
Regulatory Pathway(s)	505(b)(1), 505 (b)(2), 351(a)	505(j)	351(k)	351(k)(4)
Application Type(s)	NDAs, and BLAs	ANDAs	BLAs	BLAs
Related Human Factors Guidance for Industry	Draft Guidance for Industry and FDA Staff: Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development Released February 2016	Draft Guidance for Industry: Comparative Analyses and Related Comparative Use HF studies for a Drug-Device Combination Product Submitted in an ANDA Released January 2017	Draft Guidance for Industry and FDA Staff: Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development Released February 2016	Draft Guidance for Industry: Considerations in Demonstrating Interchangeability with a Reference Product Released January 2017

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
- Draft Guidance for Industry – Safety Considerations for Product Design to Minimize Medication Errors; http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM331810.pdf
- Draft Guidance for Industry – Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors; http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm349009.pdf
- Guidance for Industry – Label Comprehension Studies for Nonprescription Drug Products; http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm143834.pdf
- Guidance for Industry – Formal Meetings Between FDA and Sponsors or Applicants; http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm153222.pdf

Questions

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