CMC Considerations for a Successful Regulatory Submission

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Outline

- CMC Regulations and Review of INDs
- Product Development Considerations
- EOP2 Meetings
- preNDA Meetings
- Helpful Strategies for Meetings
- Useful Guidance Documents

Regulation

- **21 CFR 312.23(a)(7)(i)**
  - As appropriate for the particular investigations covered by the IND, a section describing the composition, manufacture, and control of the drug substance and the drug product.....
  - ..... sufficient CMC information to assure the proper **identification, quality, purity and strength** of the investigational drug

CMC Information

Same for all INDS or diseases, however,

- Regulations emphasize the graded nature of CMC information needed in an IND

- The amount of CMC information needed varies according to type of trial
  - Phase, Size and Duration of clinical trial, Dosage form, Prior Usage, History, etc.

- FDA recognizes that CMC development parallels clinical investigations

CMC Review at IND Stages

Primary objective is to assure the safety of patients, during all phases of the IND

Phase 1 CMC evaluated mainly from the point of **risk** to patient.

Phase 2 and 3 CMC evaluates safety, and additionally the **linkage** of the clinical test product to the to-be-marketed product

Post Phase 1 CMC Submissions

- Continue to provide CMC data to support clinical studies
- Develop data for future NDA submission
  - Demonstrate that the to-be-marketed drug has the same/similar identity, quality, purity and strength as that of the investigational drug proven to be effective and safe through clinical studies
  - Demonstrate consistency and reliability of drug manufacturing process over product life

Development Elements – ICH Q8

1. **Quality Target Product Profile (QTPP)**
   - Intended use
   - Route of administration
   - Dosage form
   - Delivery
   - Bioavailability
   - Strength
   - Container closure
   - Stability

QTPP Example

Pediatric Suspension for oral administration

How is the product used? Who will use it?

- Palatability/Taste masking
- Concentration
- Dose amount for various age groups
  - Dosing accuracy
- Deliverability
- Container and Delivery device
- Easy to use or understand instructions

(Drug product quality – drug release, stability, etc)

Development Elements (contd)

2. Identify Critical Quality Attributes (CQA) of the drug product, drug substance and excipients

- For manufacture
  - Particle Size, Polymorphic Form, ...
- For performance
  - Dissolution/disintegration, ...
- For stability
  - Water content, light protection, impurity control

Development Elements (contd.)

3. Control Strategy

- Control of drug substance
- Control of excipients and intermediates
- Process controls
- In-process testing
- Container closure system
- Drug product specification

Development Elements (contd.)

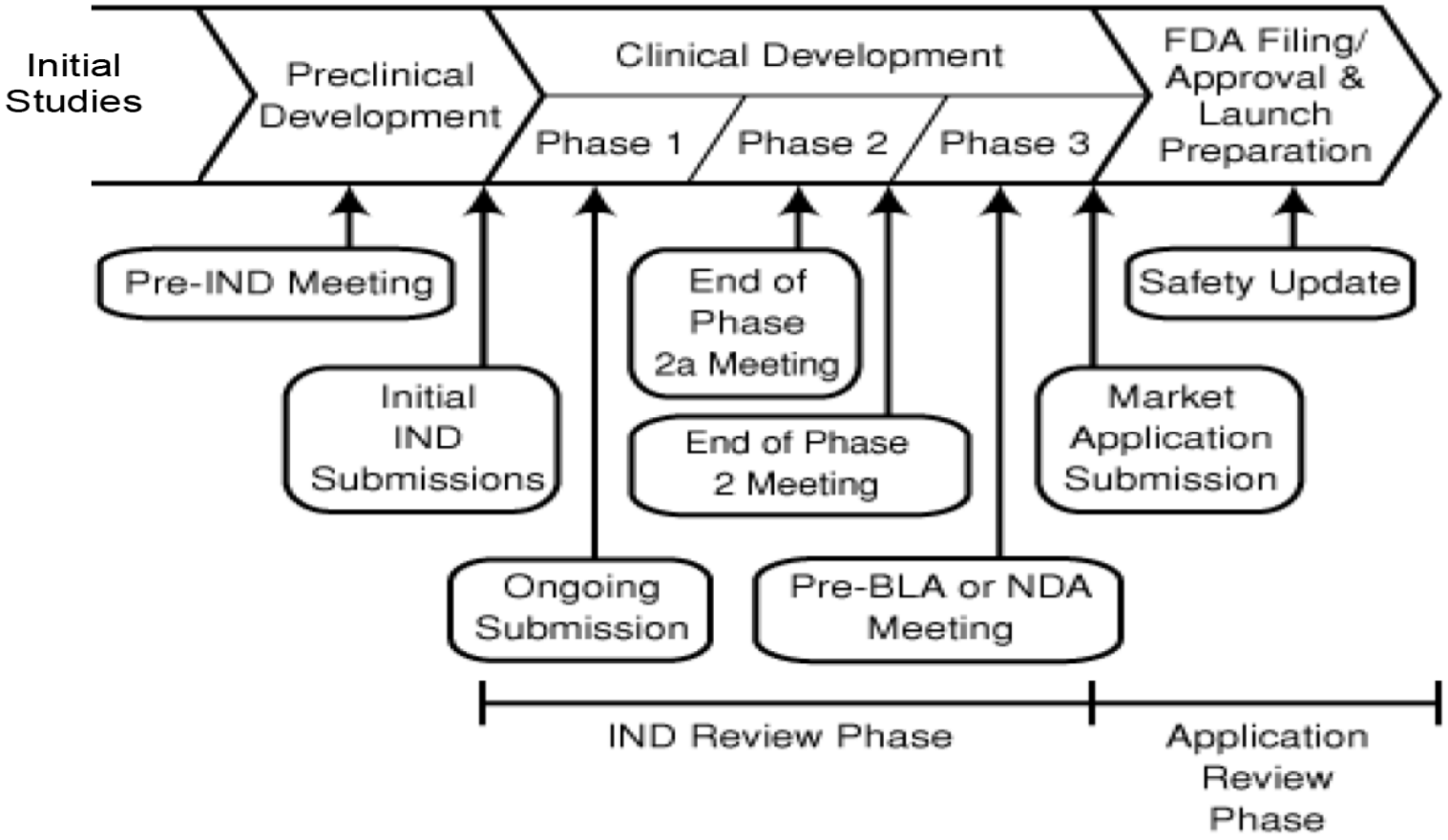
4. Manufacturing process

- Systematic and thoughtful design incorporating QTPP, CQA, etc., elements
- Process improvement and control
- Process robustness

Other Development Considerations

- QbD is not required, but can be useful. If QbD,
  - Request meeting per "*Formal Meetings Between the FDA and Sponsors or Applicants*" guidance
  - Clearly state CMC QbD meeting
- Timing Suggestions
  - EOP2 to start discussions about QbD approaches
    - Not all details or data are expected to be available
    - Discuss desired or expected approach
    - Ask specific questions, not "Does the agency agree with our approach to QbD?"
  - Pre-NDA to discuss format and details of a QbD containing submission

IND Development Milestones



EOP2 Meetings

- EOP2 meetings can be multi-disciplinary, clinical only or CMC only
- If significant CMC issues are to be discussed, a CMC only EOP2 meeting can be requested
- CMC only EOP2 meeting should be held soon after or before the clinical EOP2 meeting, prior to Phase 3 activities

CMC Perspective at EOP2

- Purpose of EOP2 CMC discussion is to
  - Evaluate CMC development results to date
  - Discuss sponsor's plans
  - Identify and resolve potential problems
  - Ensure that meaningful data will be generated during phase 3 studies to support a planned marketing application.
- Focus on CMC issues related to the Phase 3 drug (and registration stability drug)

Importance of EOP2 Meeting

- CMC discussion at EOP2 is particularly important for
  - NME
  - Complex dosage forms (Transdermals, Inhalation,...)
  - Drug-device systems
  - Biological, Botanical or Fermentation drugs
  - Complex or novel manufacturing
  - Dissolution
  - Complex QbD approaches
  - Anything unusual
- Recommend not skipping CMC discussion at EOP2 stage

Examples of CMC Issues Discussed at EOP2 Meeting

1. Agreement on starting materials
   - Complete information on s.m. such as synthesis scheme, specifications, s.m. impurities, fate and removal of s.m. impurities, DS data

2. Polymorphs, enantiomers or other unique physicochemical properties
   - Reasons for selection, stability, physicochemical properties of various forms

Examples of EOP2 CMC Issues (contd.)

3. Impurities
   - Batch data
   - Linkage to toxicology batches

4. Assay/Potency
   - Fermentation derived products, biologics, botanicals

5. General approach to specifications
   - Specs are reviewed and finalized during NDA

6. Stability protocols for Phase 3 and NDA
   - 12 months long term, 6 months accelerated

Examples of EOP2 CMC Issues (contd.)

7. Dissolution
   - Discuss dissolution method development at EOP2, if not earlier. Earlier the better
   - Approach for setting specification
     - Gather complete profile data from bio batches (PK & clinical) and registration/stability batches
     - Specifics vary for Immediate, Extended, Controlled Release and Enteric-Coated products
     - Extended Release (ER)
       - If ER claim appropriate
       - Alcohol dose dumping

Examples of EOP2 CMC Issues (contd.)

8. Anticipated manufacturing site changes
   - Impact of change (Equipment, process/parameters, product quality,..)
   - preNDA stage often too late for discussion of Ph 3, registration stability and commercial site changes

9. Link formulations/dosage forms used in Tox, PK/PD, Clinical studies conducted to date

10. Issues related to sterility and sterilization process validation

Examples of EOP2 CMC Issues (contd.)

11. Devices or Delivery System
    - Particularly for inhalers, pen injectors, transdermals, novel forms, etc
    - May recommend Ph 3 and marketed device be same

12. Placebo/Comparator Information
    - Over-encapsulation issues (e.g. dissolution)
    - Blinding information (appearance, taste, smell,....)
    - Composition, manufacture and controls

preNDA Meetings

- PreNDA purpose is to discuss filing and format issues for submission of a well-organized and complete NDA
- Questions are to confirm that all activities necessary for NDA submission are on track for the upcoming NDA
- Ideal time-frame
  - About 6 months prior to NDA submission

preNDA Discussions
(other than format issues)

1. Confirm linkage between Phase 3 and Commercial product
   - Manufacturing, Formulation, Packaging
2. Confirm issues discussed at EOP2/later stage are adequately addressed
   - Completion of any bridging studies discussed at EOP2
3. Dissolution
   - Dissolution information package in the NDA
   - Any issues not discussed during EOP2

preNDA Discussions (contd.)

4. Starting Material agreement (if not at EOP2)
5. DMFs and NDA activities are in order
6. Confirm stability data are in accordance with EOP2 agreement
7. Confirm that facilities will be ready for inspection
8. Identification of any other potential problems

Significant Changes

- Do not wait until preNDA stage to discuss
  - Significant manufacturing process changes
    - Impact of change on DP performance, manufacturability and quality
    - Comparison of processes and batch analyses information
  - Manufacturing facility changes and bridging studies
  - Stability data package changes
- If these issues arise after EOP2, a follow-up meeting during Phase 3 stage may be warranted

Helpful Strategies for Meetings

- Deliver packages at least 30 days before meeting
- Clearly identify location of each question and related background material
  - Comprehensive Index and page numbers
- Ask specific and focused questions
  - Questions related to NDA approval/acceptance cannot be answered prior to review of the entire NDA
  - Postpone question if supportive information unavailable

Helpful Strategies for Meetings (contd.)

- Concise, but comprehensive background information in the submission
  - Give a clear, scientific rationale with supporting data for position taken
  - Common problems are
    - Partial, incorrect or unrelated information
    - Lack of scientific rationale
  - Full information needed for a thoughtful response
- Avoid new questions during review or on receipt of the preliminary response

Useful Guidance Documents

- Content and Format of INDs for **Phase 1** Studies of Drugs, Including Well-Characterized, Therapeutic Biotechnology-Derived Products
- INDs for **Phase 2 and Phase 3 Studies**, Chemistry, Manufacturing, and Controls Information
- **cGMP for Phase 1** Investigational Drugs
- IND **Meetings** for Human Drugs and Biologics
- ICH Q8, Q9, Q10

Conclusions

- Graded nature of CMC information from Phase 1 to Phase 3
- Systematic pharmaceutical development (ICH Q8,Q9, Q10 principles)
- Make use of milestone meetings for early discussion of CMC or regulatory problems
- Careful selection of questions
- Concise and complete meeting packages

Thank You and Good Luck!

Questions, comments, concerns

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