Part 2
Communication is KEY!

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Outline

- Part 1: Know your product
  - Overview of range OBP products
  - Review principles and development challenges
- Part 2: Communication is Key
  - Communication strategies and approaches
  - Common product quality topics discussed with FDA
  - Case studies

Key points

- Why communicate…
- When to communicate…
- How to communicate…
- What to communicate…

Why communicate with the FDA?

- Receive regulatory feedback on CMC strategies
- Identify and avoid potential pitfalls/road-blocks
- Exchange ideas, discuss novel approaches
- May result in more efficient and robust development programs

When to communicate with the FDA?

- Any time during drug development
- Recommended at critical milestones
- Major changes or unique strategies
- Consider your development timeline

How to communicate with the FDA?

- PDUFA
  - Type A: meeting to help an otherwise stalled product development program proceed
  - Type B: Pre-IND, EOP1, EOP 2, pre-phase 3, pre-BLA
  - Type C: any meeting other than Type A or B regarding product development and review
- BSUFA – A similar formal meeting format is available for biosimilar product development

How to communicate with the FDA?

- CDER/OPQ Emerging Technology Program (ETP)
  - Promotes the adoption of innovative approaches to pharmaceutical product design and manufacturing
  - Focused on the Quality section of applications only (CMC/facility-related)
  - Submit a Type C meeting request and related questions to CDER-ETT@fda.hhs.gov

How to communicate with the FDA?

- CDER/OPQ Emerging Technology Program (ETP)
  - Types of technologies in the ETP:
    - Continuous Manufacturing of DS and DP
    - Multi-attribute Methods
    - Process Analytical Technologies
    - Model-based control strategies for continuous manufacturing
    - Biosensors
    - Novel dosage forms (e.g., nanomaterials, transdermal delivery systems, etc.)

What to communicate to the FDA?

- Risk-based product/process-related questions
  - Knowing your product (characterization)
  - Having a well-established quality management system
  - Understanding your goals and timelines

Common Product Quality-Related Topics

- Process development approaches (scale-up, process changes)
- Product development approaches (formulation, presentations)
- Analytical method changes

Process Development Case Study

Sponsor Question:

We plan to implement process changes to support initiation of our phase 2 clinical study and for future commercial material:

- New cell bank
- Increase production scale
- DS manufacturing site transfer
- DP fill volume and packaging component changes

Does the Agency agree with the overall comparability approach?

Process Development Case Study

Information Provided:

- Comparability study description:
  - Brief description of changes
  - Number of pre- and post-change DS lots proposed
  - In-process samples proposed to be evaluated
  - DS and DP release tests
  - Proposed characterization tests
  - Stability assessments

Process Development Case Study

FDA Response:

- The overarching comparability approach appears reasonable
- Insufficient information was provided on changes to the cell banks and how acceptability of the comparability study will be determined
- The process changes can impact virus clearance, provide information to support virus safety of the post-change process
- It is premature to comment on the adequacy of the proposed process and material to support commercial use

Process Development Case Study

Take-Aways:

- Perform a 360 degree risk-evaluation of the impact of changes on product quality
- Provide sufficient information and details to enable FDA to give you comprehensive feedback on your question
- Ask early about major changes to get feedback on areas that may have been missed

Product Development Case Study

Sponsor Question (Meeting 1):

- ABC DP is an enzyme formulated as a frozen solution
- Stability data showed reduced purity and increased subvisible particle formation
- Propose to change to a refrigerated liquid DP formulation with polysorbate (PS)

Does the Agency agree with the addition of PS to reduce aggregate/particulate formation?

Product Development Case Study

Information Provided:

- Data from long-term stability studies
- Development study results evaluating the impact of PS on aggregate and particle formation induced by force

Product Development Case Study

FDA Response:

We agree that the particle formation is a major stability problem. Your supporting data suggest improvement from the addition of PS. Recommendations for future development:

- Effect of PS on ABC activity
- Optimization of levels of PS in DP formulation
- Impact of PS on analytical methods
- Investigate potential PS-related oxidation of your product
- Implement specification for PS

Product Development Case Study

Sponsor Question (Meeting 2):

- We intended to develop ABC DP in a refrigerated liquid formulation with PS, but at higher temperatures aggregation and particle formation persist
- Plan to develop a lyophilized formulation

Does this change impact the Agency's previous advice and are there additional considerations we should be aware of?

Product Development Case Study

FDA Response:

- We have no opposition to the proposed development of a lyophilized formulation
- You should perform comparability studies between the relevant pre- and post-lyo batches and submit to the IND prior to initiating clinical studies with the lyo DP
- The previous advice remains applicable

Product Development Case Study

Take-Aways:

- Ask early and follow-up
- Continuous product characterization allows for risk-based product changes to be identified
- Apply previously received feedback into your continued development and communication approaches

Analytical Method Case Study

Sponsor Question:

- We are developing a cell-based ADCC assay specific for Target-1 for lot release
- Having significant development challenges
- We propose that a different potential mechanism of action of our product is initiation of ADCC activity via Target-2, and instead propose to develop a Target-2-specific ADCC reporter bioassay for release
- We do not plan to implement the potency assay as a release test prior to initiation of our pivotal study, as previously recommended by the FDA.

Does the Agency Agree?

Analytical Method Case Study

Information Provided:

- Analytical method development study report with data
- Description of the newly proposed ADCC assay
- Justification for proposed approach considering the product mechanism of action

Analytical Method Case Study

FDA Response:

- We acknowledge your efforts, but continue to recommend that a control for ADCC activity be in place for the pivotal study
- We suggest you identify alternative assay(s) that are feasible to implement as a release test until the ADCC cell-based assay is available; explore potential links between FcyR binding, glycosylation and ADCC activity
- Appropriately store retain samples from relevant clinical samples over the course of development to enable bridging and ensure batch-to-batch consistency with respect to ADCC activity
- We advise a CMC-only meeting to discuss this proposal and development plan further as data become available

Analytical Method Case Study

Take-Aways:

- Road blocks can occur
- Discuss strategy early (prior to pivotal studies) to ensure these road blocks don't result in significant issues as product development progresses
- Receive feedback on potential alternative approaches
- Have CMC-only meeting to target specific product quality-related issues

Communication Tips

- Knowing your product helps target what you want to ask
- Focus questions and ensure they are appropriate based on phase-specific considerations
- Provide sufficient information to enable a comprehensive response from FDA
- Learn from your communications and follow-up
- Purposefully utilize available communication tools

Guidance Resources

- Guidance for Industry: Formal Meetings Between the FDA and Sponsors or Applicants (2009)
- Guidance for Industry: Formal Meetings Between the FDA and Sponsors or Applicants of BsUFA Products (2018)
- Guidance for Industry: Advancement of Emerging Technology Applications for Pharmaceutical Innovation and Modernization (2017)
- Guidance for Industry and Review Staff: Best Practices for Communication Between IND Sponsors and FDA During Drug Development (2017)

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