Regulatory Tools to Support Early Access

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Overview

Mechanisms for Communication with FDA about CMC (quality) topics

- Communicate throughout all stages of product development
- Opportunities for enhanced communication after Breakthrough or RMAT designation
- Communication after licensure

CMC approaches during expedited development

Opportunities for communication throughout development

Novel products & rapid timelines → **Increased need for feedback from regulators during CMC development**

- Engage FDA CMC team throughout the product lifecycle
- Communication is especially important for:
  - Topics that lack published guidance
  - Special circumstances

Outline of the next few slides

- General enquiries
- Meetings with FDA before and during IND
  - Breakthrough or RMAT → more interaction
- Communication via amendments to IND, BLA or NDA

General advice

CBER – Manufacturers Assistance and Technical Training Branch

https://www.fda.gov/BiologicsBloodVaccines/ResourcesforYou/Industry/ucm620156.htm

CDER – Small Business and Industry Assistance

https://www.fda.gov/Drugs/DevelopmentApprovalProcess/SmallBusinessAssistance/ucm053133.htm

When to use these channels

If unsure who to contact

To request that FDA hold a liaison meeting with industry

Finding webinars and guidance documents

Meetings with FDA

Meetings may be face to face, teleconference, or written response

FDA generates official non-binding meeting minutes

Type A Stalled development or dispute

Type B Pre-IND, pre-NDA, pre-BLA, Breakthrough/RMAT

Type B(EOP) End of phase meeting

Type C All other meetings

Meeting Type	Meeting Scheduling or Written Response Time
A	30 calendar days from receipt of meeting request
B	60 calendar days from receipt of meeting request
B(EOP)	70 calendar days from receipt of meeting request
C	75 calendar days from receipt of meeting request

Interactions before an IND

INTERACT meeting (new program, CBER only)

- Early advice for pre-clinical studies or CMC issues that need to be planned well in advance
- Informal, non-binding, no written meeting minutes
- Will try to schedule teleconference within 90 days
- https://www.fda.gov/BiologicsBloodVaccines/ResourcesforYou/Industry/ucm611501.htm

Pre-IND meeting

- Type B meeting
- Written meeting minutes issued

Communication during investigational phase

Meetings for major topics and major developmental milestones

- Benefits of Breakthrough and RMAT designation:
  - Intensive guidance on efficient drug development
  - Involvement of senior managers

Routine amendments to the IND

- May be faster than a formal meeting in many cases
  - …. may be slower in other cases (workload priorities)
  - In some situations, FDA may prefer a formal meeting
- Communication via amendments allows plans and protocols to be revised through several iterations, if needed
  - For example: comparability protocols, potency assay, stability protocols

Parallel scientific advice (EMA/FDA)

- Meeting scheduled around 60 days after request
- Either full joint meeting or “consultative advice”

Communication during and after review of a license application

During application review

- Applicant orientation meeting (optional)
- Mid-cycle communication / late-cycle meeting
- Ad hoc teleconferences, if needed
- Submit amendments in response to FDA requests

Continued communication after licensure

- Supplement and amendment submission
- License holder can request meetings
- Ad hoc teleconferences may be an option

CMC approaches during expedited development

Essential goal: Ensure the availability of a quality product at time of approval

FDA may exercise some flexibility on the type and extent of manufacturing information that is expected at the time of submission and approval for certain components. Case by case, dependent on:

- Product characteristics
- Seriousness of condition and medical need
- Manufacturing processes
- Robustness of quality system
- Strength of the risk-based quality assessment

Examples of potential flexibilities

- Stability updates
- Validation strategies
- Inspection planning
- Manufacturing scale up
- Use of post marketing commitments

Examples of flexible CMC approach

Stability

- Special protocol assessment (rarely used)
- Note: ATMPs are out of scope for ICH Q5C
  - Prior knowledge / supporting data may be relevant (example: frozen products)

Concurrent release of PPQ batches for distribution before completion of process validation

- Might be applicable in rare cases, such as:
  - Limited demand / limited manufacturing
  - To alleviate short supply

Priority review

- 8 month review, instead of 12 months

Rolling NDA or BLA

- Submission of portions of application
- Note: Module 3 must be complete at the time of NDA/BLA submission

Examples of flexible CMC approach: Post-licensure

Comparability protocol (equivalent to PACMP)

- Formal plan to implement specific future manufacturing changes and analyze impact on product
- May lower the reporting category for post-approval change and allow faster implementation of the change
- Can be submitted in NDA/BLA, or after licensure as a PAS

For licensed autologous cell therapies:

- In EU, OOS batches may be released and administered under certain circumstances
- In US, OOS batches **cannot** be distributed commercially
  - May still be possible to use as investigational drug under IND

Summary

Communicate early and often about CMC

- Milestone meetings
- Breakthrough and RMAT meetings
- Amendments

Flexible CMC approaches may be applicable to expedited development programs

- A licensed product must still be high quality
- Applying flexibilities requires significant discussion with FDA

Relevant FDA guidances

1. **Formal meetings between the FDA and sponsors or applicants of PDUFA products** (Draft, 2017)
2. **IND meetings for human drugs and biologics: Chemistry, manufacturing, and controls information** (2001)
3. **Expedited programs for serious conditions – drugs and biologics** (2014)
4. **Expedited programs for regenerative medicine therapies for serious conditions** (Draft, 2017)
5. **General principles: EMA-FDA parallel scientific advice (human medicinal products)** (2017)
6. **Comparability protocols for human drugs and biologics: Chemistry, manufacturing, and controls information** (Draft, 2016)
7. **Process validation: General principles and practices** (2011)
8. **Chemistry, manufacturing, and controls changes to an approved application: Certain biological products** (Draft, 2017)
9. **Special protocol assessment** (2018)

CBER Contact Information

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- **References for the regulatory process for OTAT**
  http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/OtherRecommendationsforManufacturers/ucm094338.htm

- **OTAT Learn Webinar Series:**
  http://www.fda.gov/BiologicsBloodVaccines/NewsEvents/ucm232821.htm

CBER Contact Information

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