CMC Regulatory Expectations for Biological Therapeutic Products for Life Cycle Management and EUA Applications, a CDER/FDA Perspective

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Disclaimer

The views presented today do not represent official FDA policy, but rather represent my opinion based on my experience as a reviewer at the FDA. The views and opinions expressed here should not be used in place of regulations, published FDA guidances, or discussions with the Agency.

Pharmaceutical Quality

A quality product of any kind consistently meets the expectations of the user.

Drugs are no different.

Pharmaceutical quality is assuring every dose is safe and effective, free from contamination and defects.

Biological therapeutic products

- Monoclonal antibodies (including BsAbs, conjugates, scaffold proteins)
- Therapeutic enzymes
- Insulins and recombinant growth hormones

  - FDA guidance: The “Deemed to be a license” Provision of the BPCI ACT: Questions and Answers” March 2020

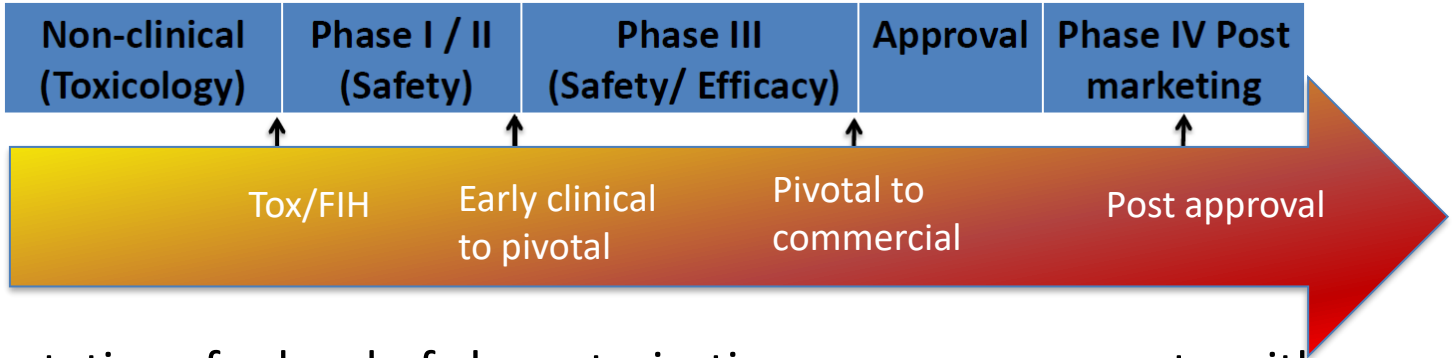
- Biosimilars:

  - Since program inception and as of April 1, 2021, 15 companies have publicly announced submission of 45 351(k) BLAs to US FDA. Twenty-nine 351(k) BLAs for biosimilar products have been approved.

Outline

- CMC considerations in different phases of development
- Analytical comparability considerations in life cycle management
- CMC approaches for COVID-19 neutralizing mAb development under Emergence Use Authorization (EUA)

CMC Development and Analytical Comparability



- Expectations for level of characterization are commensurate with:
  - Stage in lifecycle
  - Extent of change
  - Potential impact of change on safety and efficacy
  - Product and process knowledge
  - Suitability of available analytical methods
- Make major changes during development before pivotal studies
- Save pre-change materials, clinical samples, and well characterized Reference Standard. Store samples under appropriate conditions

General CMC considerations in IND development

- For initiation of a Phase I study, product safety is the first and utmost consideration (e.g., viral clearance, cell bank and unprocessed bulk testing)
  - *Guidance for Industry: Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-derived Products (https://www.fda.gov/media/72057/download)*
- Potency assay development for release control
- Product characterization and analytical method qualification
- Scale up and analytical comparability
- Reference standard bridging and qualification
- For biosimilars, preliminary Comparative Analytical Assessment data are expected in the IND submission

Post approval CMC changes

- Analytical method transfer and addition of manufacturing facilities
- Facility status, production schedule, and testing site readiness for inspection
- Post approval CMC change supplement reporting categories (e.g., PAS, CBE30)
- Comparability protocols (CP)
  - Typically used post-approval with extensive process and product knowledge
  - 21 CFR 601.12 (e) and 21 CFR 314.70 (e)
  - CP submitted as PAS; Typically reduced reporting category (CBE) for implemented changes
  - Can be used for a specific change, multiple related changes, or multiple products
  - Frequently approved for manufacture of new WCB, RS, resin & membrane reuse
  - Used to add new DS/DP manufacturing sites
  - Benefits: expedited product distribution, flexibility and planning in managing drug supply

CMC approaches for COVID-19 neutralizing mAb development

- CDER COVID-19 pIND and IND process
  - A thorough pIND meeting package and discussion between the sponsor and FDA can lead to a more rapid review of the IND

    See the Guidance for Industry and Investigators "COVID-19 Public Health Emergency: General Considerations for Pre-IND Meeting Requests for COVID-19 Related Drugs and Biological Products" (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/covid-19-public-health-emergency-general-considerations-pre-ind-meeting-requests-covid-19-related) (May 2020)
- OBP flexibility for neutralizing antibodies to enter Phase 1 clinical trials under the pandemic situation
- This CMC flexibility is contingent upon sufficient information being shared with FDA

OBP Flexibility to Expedite Entry of Neutralizing mAbs into Phase 1 Trials

- Principles laid out in the 1997 Points to Consider in the Manufacture and Testing of Monoclonal Antibody Products for Human Use
  - Reduced safety testing for feasibility clinical trial in serious or life-threatening conditions
  - Generic/modular virus clearance studies or
  - Two orthogonal robust virus clearance steps
- Platform processes and prior knowledge may provide support for less information than typically submitted in a non-pandemic IND
- Risks for comparability between lots produced from stable pools and MCB
- Deferral of certain cell substrate and product testing

OBP Flexibility to Expedite Entry of Neutralizing mAbs into Phase 1 Trials – Potency Assays

- Use of target binding assay for release and stability to initiate IND with expectation to develop a relevant cell-based potency assay as clinical development progresses
- Pseudotyped virus- or VLP-based assays are considered relevant for the purpose of release and stability testing
- All mAbs should be characterized for antibody effector functions

Guidance for Industry:
COVID-19: Potency Assay Considerations for Monoclonal Antibodies and Other Therapeutic Proteins Targeting SARS-CoV-2 Infectivity | FDA (Jan. 2021)
Development of Monoclonal Antibody Products Targeting SARS-CoV-2, Including Addressing the Impact of Emerging Variants, During the COVID 19 Public Health Emergency | FDA (Feb. 2021)

CMC considerations for mAb EUA

- CMC data when available can be submitted to the IND for review; when submitting EUA, module 3 can cross reference to the IND
- Drug substance characterization, including primary, secondary, and higher order structure, established and/or potential MOA(s), product- and process-related species
- Detailed description of the drug substance/drug product manufacturing process, including critical raw materials, process parameters, and overall control strategy
- Status of process qualification/validation and plans for process qualification/validation

Additional CMC considerations for mAb EUA (Cont'd)

- Drug substance/drug product release and stability specifications and their justification
- Available analytical method qualification/validation data, as appropriate.
- Analytical data for all lots/batches manufactured to date, along with information regarding how the lots were used
- Data to support comparability between materials used in clinical studies to support a role for the product in treating COVID-19 and the proposed materials to be used under EUA
- Drug substance/drug product **stability** (Proposed expiry and long-term storage conditions; stability protocol(s); data to support proposed expiry and possible expiry extension, as applicable)

Additional CMC considerations for sterile DP under EUA

- For sterile drug products:
  - Aseptic filling process including the manufacturing areas/classification and type of fill line, sterilizing filtration parameters, filter integrity testing, process and filtration hold times
  - Product contact equipment and components, and container closure system with the corresponding method(s) of sterilization and depyrogenation
  - Media fill study and summary of additional supporting studies performed to date

- Control of drug product excipients in-use stability/compatibility study results to support drug product handling, preparation, and administration

- Flexible in use conditions for EUA products require appropriate supporting CMC data

- Production capacity (e.g., number of doses per month or quarter)

CMC changes post Emergency Use Authorization

- Submit CMC data supporting changes of manufacturing processes and addition of facilities to the IND; Analytical comparability data are expected
- Facility cGMP compliance and inspection readiness for addition of manufacturing facilities
- Deviation reporting (Conditions in Letter of Authorization)
- Stability data updates
- Fact Sheets updates (e.g., change of in-use condition, or infusion time, or neutralizing activities against emerging variants)

Summary

- CMC data and phase-appropriate comparability exercises are expected during biological product life cycle management
- Major manufacturing changes post pivotal trial (or post approval) will need to be supported by comprehensive comparability studies and/or validation; certain changes (e.g., change of MCB) post-approval may need additional PK or clinical data to support besides CMC
- Certain CMC flexibilities are exercised to expedite COVID19 neutralizing mAbs to enter phase 1 under the pandemic
- To facility CMC change management under EUA, meet with agency in advance

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Thank you for your attention

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