Chemistry, Manufacturing, and Controls Assessment for Expedited Programs

Paresma R. Patel, Ph.D.
Division Director
Division of New Drug API, Office of New Drug Products
CDER | US FDA

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Learning Objectives

- Describe PDUFA VII Product Quality Enhancements
- Name common regulatory strategies to address CMC challenges under expedited programs
- Understand the CMC Development and Readiness Pilot (CDRP) Application Process, Eligibility, and Selection Criteria

Outline

- Product Quality Overview
- Facilitating CMC Readiness for Products with Accelerated Clinical Development
  - Quality Assessment for Products in Expedited Programs (MAPP 5015.13)
  - CMC Development and Readiness Pilot (CDRP), CDER Perspective
- Summary and Resources

A quality product of any kind consistently meets the expectations of the user – drugs are no different.

Patients expect safe and effective medicine with every dose they take.

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

It is what gives patients confidence in their *next* dose of medicine.

Quality Assessment for Products in Expedited Programs (MAPP 5015.13)

Quality Assessment for Products in Expedited Programs

- CMC development for CDER-Regulated Products
  - Products with accelerated clinical development timelines: breakthrough, fast track, and CMC Development and Readiness Pilot (CDRP)
  - Mission critical products: addressing public health emergencies with no available treatment, drug shortages, orphan drug designation
- Regulatory flexibilities to address CMC challenges
- Early engagement with sponsors
- Use of science- and risk-based approaches
- Anticipated clinical benefit of earlier patient access

OPQ Assessment for Expedited Programs

- Office of New Drugs (OND) identifies products that qualify for expedited designation
- OPQ assessment team for expedited programs:
  - Participates in Type B, Type C, and Type D industry meetings
  - Determines progress in product development and plan for commercial manufacturing
  - Reviews strategy to ensure commercial facilities are ready for manufacturing
  - Identifies regulatory opportunities to expedite CMC development
  - Considers data and information to be submitted and timing
  - Establishes a communication plan for future interactions and regulatory approaches

Facility Readiness

Early and enhanced communication for facility assessments

- Identification of intended commercial facilities
- Any non-commercial facilities to support marketing application approval
- Cross-referenced applications (Type II DMFs) and letter(s) of authorization
- Commercial manufacturing process and comparison to clinical process
- Plans to ensure commercial facilities are cGMP compliant
- Plans for commercial launch, if atypical
- Submission strategy and timing for facility information (Form 356h)
- Manufacturing schedule and production schedules for BLAs

Office of Pharmaceutical Manufacturing Assessment works with Office of Regulatory Affairs to assess facilities and make recommendations

Regulatory Flexibility Options

- Control Strategies
- Process Validation
- Analytical Procedures
- Marketing of batches manufactured with clinical manufacturing process
- Stability data and studies

Control Strategies

- Flexibility based on totality of product and process understanding
- Demonstrating thorough understanding of product, manufacturing process, analytical capabilities helps FDA consider alternative approaches
- Justification of commercial control strategy and benefit-risk considerations will be assessed
- There may be limited manufacturing and clinical experience
  - Additional specification tests, in-process testing, narrower or wider acceptance criteria and process parameters
  - Comparability protocols to address changes post approval
  - Post-marketing commitments to revise methods once more knowledge and experience is available

Process Validation

Alternate approaches to Stage 2 Process Validation should be discussed early in CMC-focused meeting

- Certain CMC confirmatory studies postapproval
- Decoupling validation of drug substance and drug product processes
- Concurrent validation/concurrent release (CV/CR) approaches

Analytical Procedures

- Analytical procedures consistent with requirements under 314.50(d)(1), and 601.2(a), 601.2(c)
- Control strategy is acceptable for approval
- Changes needed to method validation may be implemented postapproval (e.g., a CMC PMC)

Marketing with Clinical Batches

- Scale-up of clinical manufacturing process will delay commercial launch
- Commercial distribution with batches from clinical-scale manufacturing process and facility
  - Identify manufacturing facilities
  - Any material for commercial distribution will meet FDA standards
  - Facility readiness for inspection, if needed
  - Reminders about Stage 2 process validation requirements
  - Scaling up of the manufacturing process postapproval can be facilitated by Comparability Protocols
  - Postapproval commitments to complete scale-up activites

Marketing with Clinical Batches

Proposals to commercially distribute stockpiled clinical batches

- Facility that manufactured stockpiled clinical batches will be listed as commercial manufacturing facility
- Manufactured using a process representative of commercial process
- Reflective of intended commercial control strategy (meet updated specifications)
- Batches will be distributed with approved labeling

Stability Studies

- Consideration of all available data (process and product understanding, supportive stability data, prior knowledge)
- If an alternate approach will be proposed:
  - Discuss stability strategy for shelf life and/or retest with OPQ early (e.g., CMC-focused meeting)
  - Aim to seek agreement at or before pre-NDA/pre-BLA meeting
    - Proposed stability strategy
    - Data and information at filing and during review to support approval

Stability Studies

- Regulatory flexibility examples
  - Less than recommended data for primary stability batches at submission
  - Additional stability data submitted during review
  - Data from batches that differ in size
  - Supportive stability data
    - May be helpful to establish retest or shelf life
    - OPQ assesses comparability to ensure batches are representative of commercial batches and process

Predictive Stability Models

- Modeling of stability data from drug substance and drug product to establish retest dates and shelf life for NDAs
- Establish comparability of primary and supportive stability for use of supportive data
- Evaluation of the proposed model and supportive information
  - Capability of the model to capture relevant stability factors
  - Validation data that the model's kinetic assumptions are appropriate
  - Applicability to the container closure
  - Product stability-indicating critical quality attributes were considered in establishing the model
  - Situations where the model would not be appropriate

Summary

- MAPP 5015.13 outlines quality assessment considerations and regulatory flexibilities for products in expedited programs
- Early engagement with FDA is encouraged to address CMC challenges for products in expedited programs
- **Goal:** ***provide patients with earlier access to new drugs and biologics***

Challenge Question #1

MAPP 5015.13 Quality Assessment for Products in Expedited Programs describes regulatory flexibilities for all the following, except:

A. Process Validation Approaches

B. Control Strategies

C. Stability Studies

D. cGMP Requirements

CMC Development and Readiness Pilot (CDRP), CDER Perspective

CMC Development and Readiness Pilot (CDRP) Background

- Development of CDER-regulated drugs where there is unmet medical need often have accelerated clinical development timelines
- Marketing applications for products in expedited development programs still need to meet FDA's approval standards
- Products with accelerated clinical development may face challenges expediting CMC development activities
- Goal is to facilitate CMC development of products with accelerated clinical development timelines
  - Additional interactions with FDA during development
  - Science- and Risk-based regulatory approaches
  - Streamlining CMC development
  - Earlier patient access to products

Federal Register Notice (FRN)

8 – 10 proposals accepted per year, April 2023-2027

- ~6 CBER and ***3 CDER Applications*** accepted per year

For sponsors selected to participate in pilot:

- Product-specific CMC advice during product development
- Two additional CMC-focused Type B meetings
- Limited additional CMC focused discussions
- Ensure mutual understanding of approaches to CMC (i.e., information for NDA or BLA submission)

Eligibility

- Active commercial IND in Electronic Common Technical Document (eCTD) format
- Before End of Phase 2, with exceptions
- Commitment to pursue CMC development plan that aligns with expedited clinical development
- CDER-Specific Criteria
  - Intended for approval under 505(b) FD&C or 351 (a) of PHS
  - Expedited clinical timeframe based on anticipated clinical benefits of earlier patient access (e.g., Breakthrough or Fast-track designation)
  - Sponsors of products that meet criteria may apply and eligibility determined by FDA

Request to Participate Process

- Current state of CMC development
- Projected timeline for product development that aligns with clinical development
- CMC activities to yield complete CMC data and information for marketing application
- CMC challenges that may require FDA input
- Proposed timing for two additional CMC-specific Type B meetings, if selected

Request to Participate Process

CMC Development Status and Proposed Plans

- Available product characterization and critical quality attributes
- Current drug substance and drug product manufacturing process and control strategies (bioassays, as applicable)
- Plan for proposed commercial scale manufacturing and control strategy
- Manufacturing facilities and inspection history
- Plans to ensure product availability for commercial launch
- Drug substance and drug product stability assessment plan
- Process validation plans

Selection Process & Criteria

- Review occurs quarterly (or as needed)
- Sponsors will be notified on selection within 180 days of receipt
- ~3 CDER Applications accepted per year
- Criteria
  - Anticipated clinical benefits of facilitating earlier patient access
  - Novelty of the product
  - Complexity of the product, manufacturing process, technology
  - Sponsor's overall manufacturing experience
  - Sponsor's experience with product type, class, manufacturing process

Balance and diversity in product types, sponsors, therapeutic indications

Summary

- CMC Development & Readiness Pilot (CDRP) aims to facilitate CMC development for products with expedited clinical development timelines
- Increase communication between FDA and sponsors
- CDRP started April 2023 and sponsors are invited to apply
- **Goal:** ***provide patients with earlier access to new drugs and biologics***

CDRP, CBER Perspective ReDI June 9th 2023
Dr. Ramjay Vatsan

Challenge Question #2

How many CDER CDRP Applications will be selected per year under the pilot:

A. 10

B. 6

C. 3

D. All of them

Resources for CDRP

https://www.fda.gov/drugs/pharmaceutical-quality-resources/chemistry-manufacturing-and-controls-development-and-readiness-pilot-cdrp-program

U.S. FOOD & DRUG ADMINISTRATION

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Chemistry, Manufacturing, and Controls Development and Readiness Pilot (CDRP) Program

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Pharmaceutical Quality Resources

- Chemistry, Manufacturing, and Controls Development and Readiness Pilot (CDRP) Program
- Current Good Manufacturing Practice (CGMP) Regulations
- CDER Quality Management Maturity
- Q&A on CGMP Requirements
- Inspection/Enforcement

What's New

FDA will be accepting requests to participate in the CDRP on April 1st, 2023.

Federal Register Notice

Content current as of: 03/16/2023

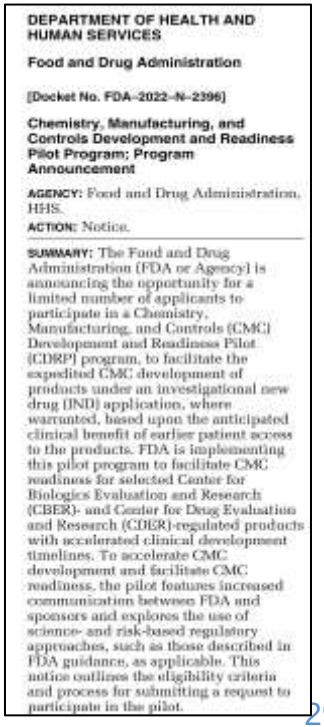
Regulated Product(s): Drugs

What is the CDRP

On October 31, 2022, FDA announced the *Chemistry, Manufacturing, and Controls (CMC) Development and Readiness Pilot (CDRP) Program* for Center for Biologics Evaluation and Research (CBER) and Center for Drug Evaluation and Research (CDER) regulated products. CBER and CDER will conduct the CDRP to facilitate CMC development of selected products under

CDRP aims to:

- Facilitate the expedited CMC development of products with expedited clinical development timeframes.



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA–2022–N–2396]

Chemistry, Manufacturing, and Controls Development and Readiness Pilot Program; Program Announcement

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA or Agency) is announcing the opportunity for a limited number of applicants to participate in a Chemistry, Manufacturing, and Controls (CMC) Development and Readiness Pilot (CDRP) program, to facilitate the expedited CMC development of products under an investigational new drug (IND) application, where warranted, based upon the anticipated clinical benefit of earlier patient access to the products. FDA is implementing this pilot program to facilitate CMC readiness for selected Center for Biologics Evaluation and Research (CBER)- and Center for Drug Evaluation and Research (CDER)-regulated products with accelerated clinical development timelines. To accelerate CMC development and facilitate CMC readiness, the pilot features increased communication between FDA and sponsors and explores the use of science- and risk-based regulatory approaches, such as those described in FDA guidance, as applicable. This notice outlines the eligibility criteria and process for submitting a request to participate in the pilot.

Resources for Quality Assessment for Products in Expedited Programs

- MAPP 5015.13: https://www.fda.gov/media/162786/download
- Benefit-Risk Considerations for Product Quality Assessments (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/benefit-risk-considerations-product-quality-assessments)
- Expedited Programs for Serious Conditions––Drugs and Biologics (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/expedited-programs-serious-conditions-drugs-and-biologics)
- ICH Guidances for Industry:
  - Q5C Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products
  - Q1A(R2) Stability Testing of New Drug Substances and Products
  - Q9 Quality Risk Management
  - Q8(R2) Pharmaceutical Development
  - Process Validation: General Principles and Practices
  - Q11 Development and Manufacture of Drug Substances
  - Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients
  - Q12 Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management

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Questions?

Paresma R. Patel
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Paresma.patel@fda.hhs.gov