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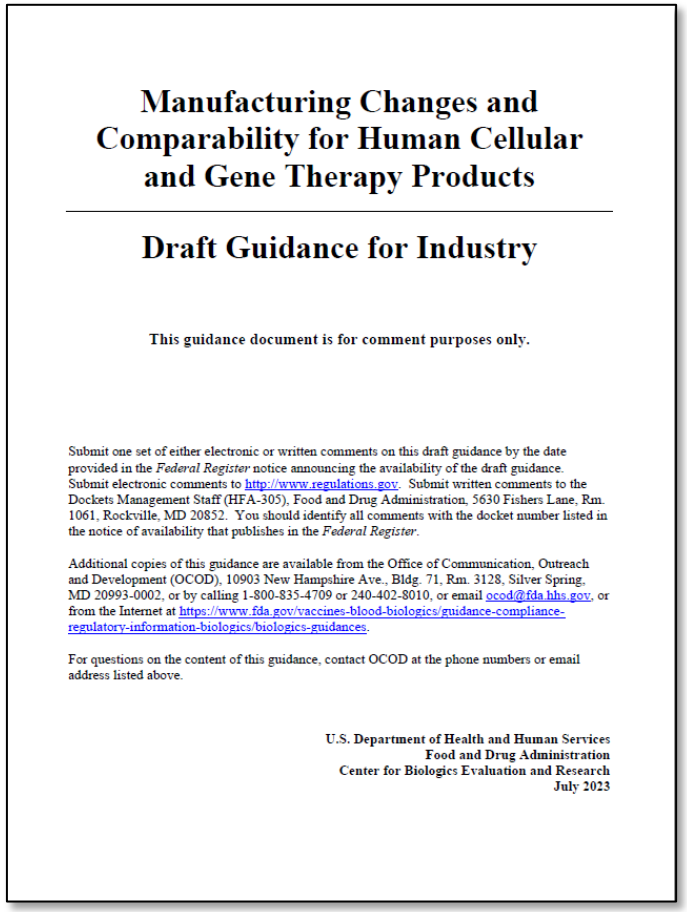
Change Management and Comparability for Cellular & Gene Therapy Products

Ingrid Markovic, Ph.D.
Senior Science Advisor
FDA/CBER

CBER ICH Quality Lead & M4Q FDA Topic Lead

2023 Draft Guidance
Manufacturing changes and comparability



Manufacturing Changes and Comparability for Human Cellular and Gene Therapy Products

Draft Guidance for Industry

This guidance document is for comment purposes only.

Submit one set of either electronic or written comments on this draft guidance by the date provided in the *Federal Register* notice announcing the availability of the draft guidance. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. You should identify all comments with the docket number listed in the notice of availability that publishes in the *Federal Register*.

Additional copies of this guidance are available from the Office of Communication, Outreach and Development (OCOD), 10903 New Hampshire Ave., Bldg. 71, Rm. 3128, Silver Spring, MD 20993-0002, or by calling 1-800-835-4709 or 240-402-8010, or email ocod@fda.hhs.gov, or from the Internet at https://www.fda.gov/vaccines-blood-biologics/guidance-compliance-regulatory-information-biologics/biologics-guidances.

For questions on the content of this guidance, contact OCOD at the phone numbers or email address listed above.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
July 2023

This draft guidance document is issued for comment purposes only

You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations

Provide advice for manufacturers of human cellular and gene therapy products regarding:

- Managing manufacturing changes and reporting the changes to FDA
  - For both investigational and licensed products
- Analytical comparability studies
  - Special considerations for cellular and gene therapies
  - Comparability study design and statistical approaches

Broad themes and highlights

Risk management

Planning for future changes

Phase-dependent expectations

Comparability studies

Obtaining advice and feedback from FDA

OUTLINE

Managing manufacturing changes

Reporting manufacturing changes to an IND or BLA

Assessing comparability

MANAGING MANUFACTURING CHANGES

Common reasons for manufacturing changes

Improving product quality

Improving efficiency or reducing costs

Adjusting to changes in the availability of materials

Expanding product supply

- Scale up
- Scale out
- New facility

Risk management

The risk of a significant manufacturing change can be high for cellular and gene therapies

- These are complex and novel products
- Risk management relies on a clear understanding of critical aspects of the product and manufacturing process

Use a formal risk management strategy

- Will enable you to evaluate manufacturing changes effectively and efficiently
- Will aid when deciding whether a comparability study is needed
  - And will guide how to design the comparability study

We recommend *Q9(R1) Quality Risk Management* for advice on how to systematically manage risk

Manufacturing changes can pose risks to product quality

It is critical that manufacturing changes do not adversely affect product quality

Changes cannot compromise the safety or effectiveness of the product

Perform a risk assessment before making manufacturing changes

Risk assessment plays a central role in quality risk management

If a change has a potential to adversely affect product quality, determine the impact of the change

Perform comparability studies to evaluate any adverse effects of the change on product quality

Phase-dependent considerations when making manufacturing changes

The extent of comparability data needed is highly dependent on:

- The stage of clinical development
- The severity and likelihood that the change might adversely affect product quality

Comparability studies and statistical approaches should typically be more rigorous later in the product lifecycle

- Changes in the middle of a pivotal study
- Changes right before a BLA submission
- Changes post-licensure

Best practices

- Develop a thorough understanding of the product's quality attributes and how the manufacturing steps affect these attributes
- When possible, implement any extensive changes before initiating pivotal studies

Challenges in managing manufacturing changes for cellular and gene therapy products

Challenges when assessing risks

- Limited characterization of the product and the manufacturing process
- Uncertain mechanisms of action and difficulty measuring potency

Challenges for comparability studies

- Variable cellular source material
- Limited cellular source material
- Limited number of lots
- Small lot size or limited sample volume
- Changes in assays

Planning ahead for changes

Plan ahead to reduce risks and disruptions from future manufacturing changes

- Develop a scalable process
- Retain sufficient samples of all lots
- Manufacture a sufficient number of lots to support future comparability studies
- Understand how changes to assays might affect your ability to evaluate comparability

REPORTING MANUFACTURING CHANGES TO AN IND OR BLA

Reporting manufacturing changes to INDs

Submit manufacturing changes that may affect product quality

- Update CMC information using IND amendments
- Submit CMC information well in advance of implementing the change
  - To allow sufficient time for FDA review and feedback
- Also summarize any significant manufacturing changes in your IND's annual report

An IND may be placed on clinical hold if:

- You make a manufacturing change with a potential adverse impact on safety or effectiveness, but you do not adequately evaluate the impact of the change

Some changes may yield a different product

Some changes fundamentally alter the design or nature of a product

- A fundamentally new product should be submitted in a new IND
- These types of changes are not amenable to comparability studies
- Please ask us if you are unsure

Examples:

- For a T cell therapy:
  - Change from CD4+ T cells to a mixture of CD4+ and CD8+ T cells
- For a gene therapy vector:
  - Change to the vector capsid that alters vector tropism
- For a genome editing product:
  - Different target gene

Reporting manufacturing changes to BLAs

Assess the potential impact of all manufacturing changes

Report the change in a supplement:

For manufacturing changes that have a substantial or moderate potential to have an adverse effect on product quality

Annual report:

For manufacturing changes that have a minimal potential to have an adverse effect on product quality

Include data to evaluate the effect of the change on product quality

An approved comparability protocol may ease implementation of a change

Submit your comparability protocol in a supplement, and we will review

ASSESSING COMPARABILITY

Obtaining advice on comparability studies

Involve a statistician when you design a comparability study

Obtaining feedback from FDA

- Prospectively discuss significant manufacturing changes
- Provide a detailed comparability protocol
- If a change needs to be made but the product is not comparable, discuss proposed clinical studies with the post-change product
- Mechanisms for obtaining feedback:
  - Formal meeting request
  - IND amendment
  - BLA product correspondence

Comparability studies, protocols and reports

Before conducting a comparability study, prospectively write a comparability protocol:

- Describe the manufacturing change
- Assess the risk of the change
- Describe the study design in detail, including which lots will be used
- List test methods and acceptance criteria
- Describe how the data will be analyzed

Submit the comparability report to your IND or BLA

Goals of an analytical comparability study

Ensure that the safety and effectiveness of the product will not be compromised by the manufacturing change

- It is not necessary for product quality to be identical after a manufacturing change
- Demonstrate that the change has no adverse effect on the safety or effectiveness of the product

Evaluate all attributes of the product that might be adversely affected by the change

- Changes to the manufacturing process can have higher risk than routine manufacturing
  - Lot release assays may not always be sufficient to evaluate comparability
  - Additional product characterization is often appropriate

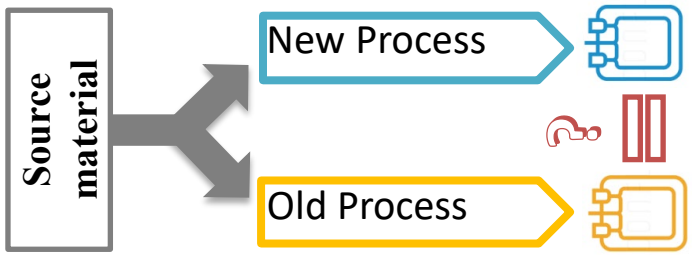
Products derived from a variable cellular starting material

Donor-derived cells are highly variable

This results in variable product attributes, which can make it difficult to evaluate how manufacturing changes affect product quality

Split-source material study design and paired statistical analysis may help

This study design can minimize the effect of source material variability



When manufacturing product for comparability studies:

Best to use the same type of source material as the clinical product

But may be able to use other material if justified
(for example, cells from healthy donors)

The comparability report

Introduction

- Description of the manufacturing changes
- Rationale and justification for the changes
- Justification of the comparability study design
- Timeline for implementing the changes

Risk Assessment

- Determine quality attributes that are at risk from the change
- Select product attributes and process parameters to be evaluated

The comparability report

Comparability Study Design

- List the lots included in the study, and sources of historical product data
- Describe the test methods
- List the acceptance criteria for comparability of each attribute
  - These should be based on understanding the relationship of the attribute to safety or effectiveness
- Refer to the draft guidance for some advice on specific situations

Results and conclusions

- Include data in tabular format, along with summary statistics
- Describe the conclusions from the study
- Explain any changes or deviations from the comparability protocol

Reaching a conclusion about comparability

A comparability study should reach a definitive conclusion

- Is the post-change product comparable to the pre-change product?

Failing to detect differences is *not* the same as demonstrating equivalent product quality

- Some comparability studies are inconclusive because of:
  - Lack of statistical power
  - Imprecise assays
  - Poor understanding of a product's quality attributes
  - Lack of assays to measure a product attribute that may be affected by the change
- A two-sample *t*-test is usually not an appropriate method

If a product is not analytically comparable after a change (or if the comparability study is inconclusive), then:

- Nonclinical or clinical studies may be needed to demonstrate the safety and/or effectiveness of the post-change product

Conclusions

- **Risk management should play a central role in managing manufacturing changes and designing comparability studies**
- **Plan ahead for future changes**
- **FDA can provide advice throughout the lifecycle (IND, BLA or post-approval)**

CMC DEVELOPMENT AND READINESS PILOT PROGRAM (CDRP)

- CMC COMMITMENT DEVELOPED UNDER PDUFA VII -

- Interesting fact: PDUFA VII is fist time CMC became part of PDUFA discussion since program inception in 1992

CDRP-Federal Register Notice (FRN)

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.

CDRP Start Date : April 1, 2023

Duration of CDRP: 2023-2027 (PDUFA VII Period)

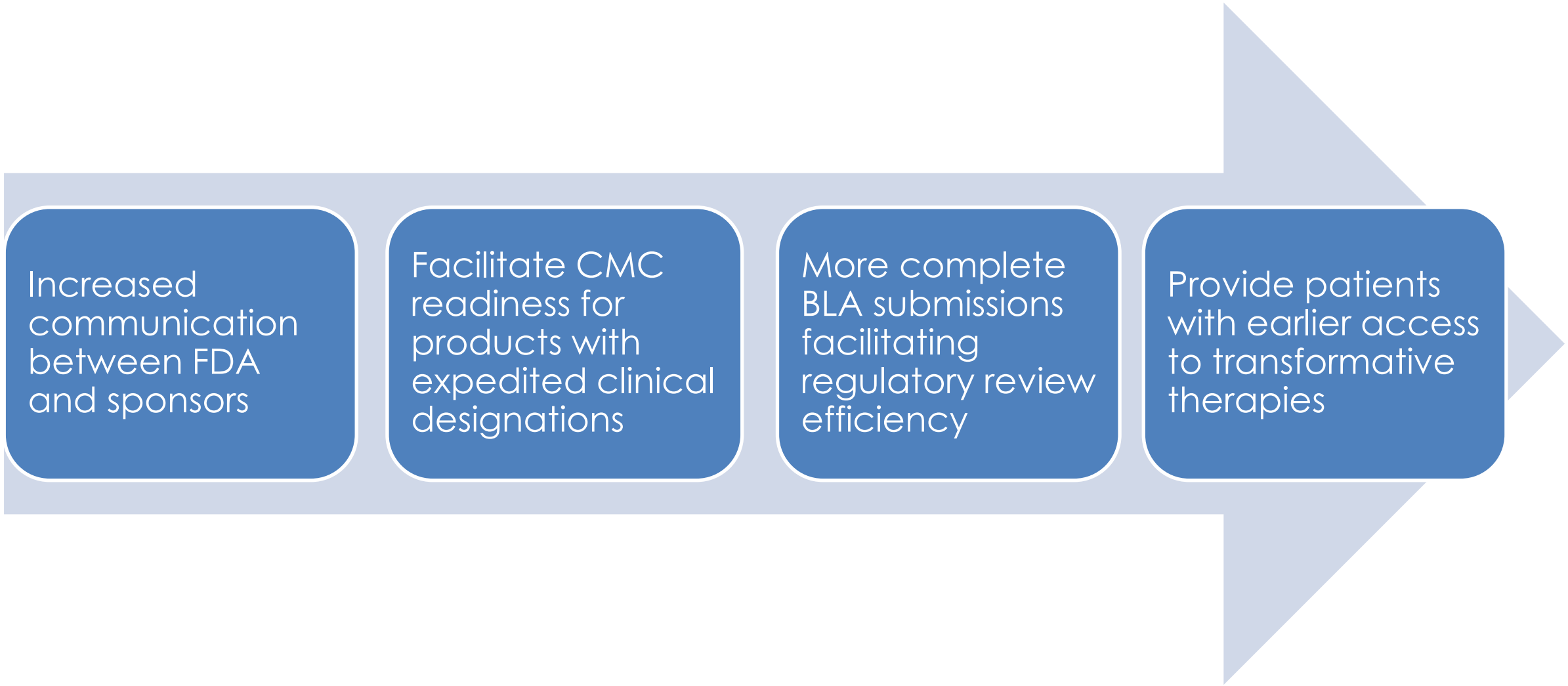
Sponsors of INDs with accelerated clinical development timelines are invited to apply to the CDRP

CDRP aims to:

- Facilitate the expedited CMC development of products
- Increase communication between FDA and sponsors
- Provide patients with earlier access to these products
- A total of 9 INDs will be selected each year (6 CBER and 3 CDER)

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

CDRP Program: Anticipated benefits



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- And many others

THANK YOU!