Manufacturing Changes and Comparability for Cell and Gene Therapy Products

CASSS CGTP Symposium: Session 1
Tuesday, June 9, 2026

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Manufacturing changes and comparability for CGTs

- Most available guidance for managing manufacturing changes focuses on well-characterized products
- While the *principles* in these guidance documents still apply to CGTs, practical implementation is difficult
- CGTs are affected by multiple unique factors which complicate the management of manufacturing changes and evaluation of comparability (*High manufacturing/product complexity, limited manufacturing experience, variable starting materials etc.*)
- New guidance for CGTs was highly sought by industry and stakeholders

ICH Q5E (2005)

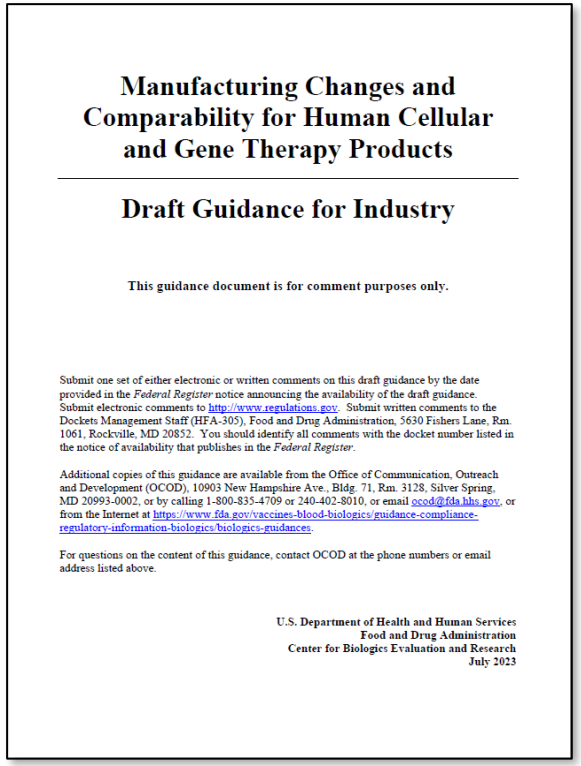
…The principles adopted and explained in this document apply to…Proteins and polypeptides, their derivatives, and products of which they are Components….[which] can be highly purified and characterized using an appropriate set of analytical procedures.

Comparability of Human Biological Products (1996)

…Manufacturers should provide to FDA extensive chemical, physical and bioactivity comparisons with side-by-side analyses of the "old" product and qualification lots of the "new" product. When available, fully characterized reference standards for drug substance and final container material should also be used.

2023 Draft Guidance on Manufacturing changes and comparability

- The FDA is in the process of finalizing the 2023 Draft Guidance on Manufacturing changes and comparability (992 comments!)
- This guidance provides advice for manufacturers of human CGTs, particularly regarding:
  - Managing and reporting changes to the FDA
  - Appropriate design of analytical comparability studies
  - Recommendations for navigating CGT-specific complexities
  - Special considerations for tissue engineered medical products (TEMPs)



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Draft Guidance for Industry

This guidance document is for comment purposes only.

Submit one set of either electronic or written comments on this draft guidance by the date provided in the *Federal Register* notice announcing the availability of the draft guidance.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

Organization

- The guidance document is arranged into three primary sections:

1. **Considerations for the <u>management</u> of manufacturing changes**
   - Quality system approach to navigate manufacturing changes
2. **<u>Regulatory reporting</u> of manufacturing changes**
   - How and when to tell the FDA about manufacturing changes
3. **Comparability assessment and report**
   - How to design and execute a comparability study

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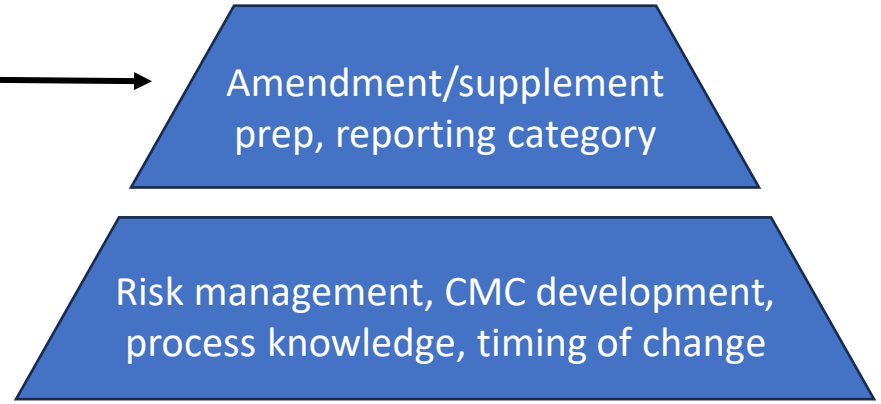

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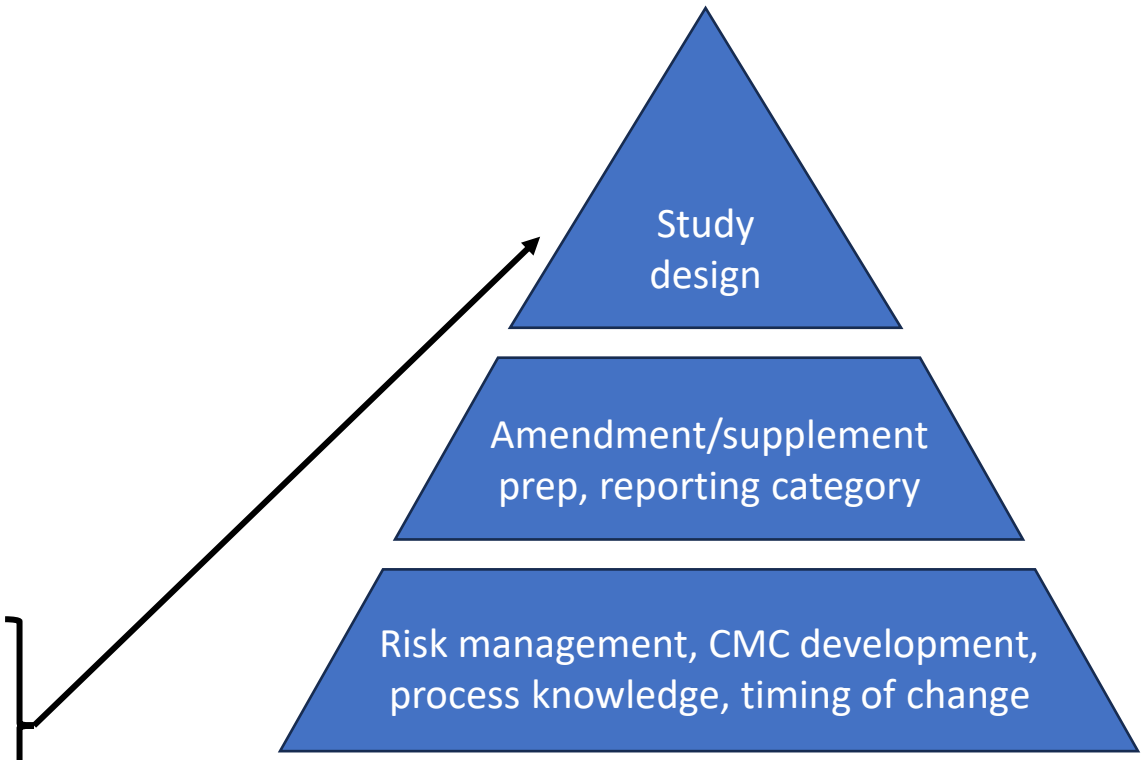


Management of Manufacturing Changes

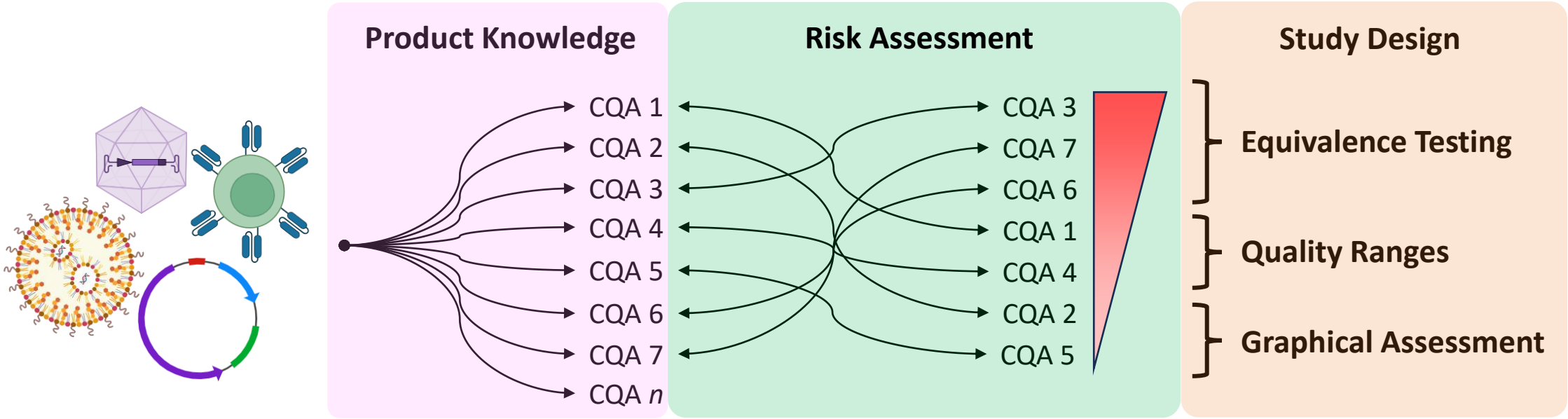
- Manufacturing changes may be introduced for several reasons including:
  - Improving product quality
  - Improving efficiency or reducing cost
  - Adjusting to changes in supply chains
  - Expanding product supply (scale up, scale out, new facility, etc.)
- CGTs may be especially sensitive to many different changes
  - The FDA recommends using a formal risk management strategy when planning manufacturing changes per *Q9(R1) Quality Risk Management*

Management of Manufacturing Changes – Risk assessment

- Accurately evaluating risk is essential, because it is critical that manufacturing changes do not adversely affect product quality
- All manufacturing changes should be evaluated with a risk assessment prior to implementation.
- This risk assessment is central to determining whether a change necessitates an analytical comparability study

Management of Manufacturing Changes – Risk assessment

- In addition to identifying the need for an analytical comparability study, a risk assessment informs how a comparability study should be designed.
- The parameters evaluated, statistical approach, and equivalence margins are all informed by the risk assessment



Management of Manufacturing Changes – Lifecycle approach

- The extent of comparability data required is highly dependent upon the stage of clinical development, and the risk that the change may adversely impact product quality
- Comparability studies and statistical approaches are typically more rigorous later in the product lifecycle due to increased risk.
  - Changes in the middle of a pivotal study
  - Changes following a pivotal study, but prior to licensure
  - Changes made post-licensure

Management of Manufacturing Changes – Phase Appropriateness

- Planning ahead may reduce disruptions from future manufacturing changes, particularly by:
  - Developing scalable processes
  - Keeping retains of all DP lots
  - Manufacturing sufficient lots to support future comparability studies
  - Developing and refining analytical methods
  - Implementing changes early, when less risk to clinical development.

Evaluating comparability – Core Goals

- The goal of the comparability exercise is to ensure that the quality, safety, and effectiveness of a drug product has not been adversely impacted by a manufacturing change
  - ➢ It is not necessary for product quality to be identical after a manufacturing change
- Evaluate all attributes that may be adversely affected by the change
  - ➢ Lot release assays may not always sufficiently capture changes to product quality
  - ➢ In-process tests may be particularly useful

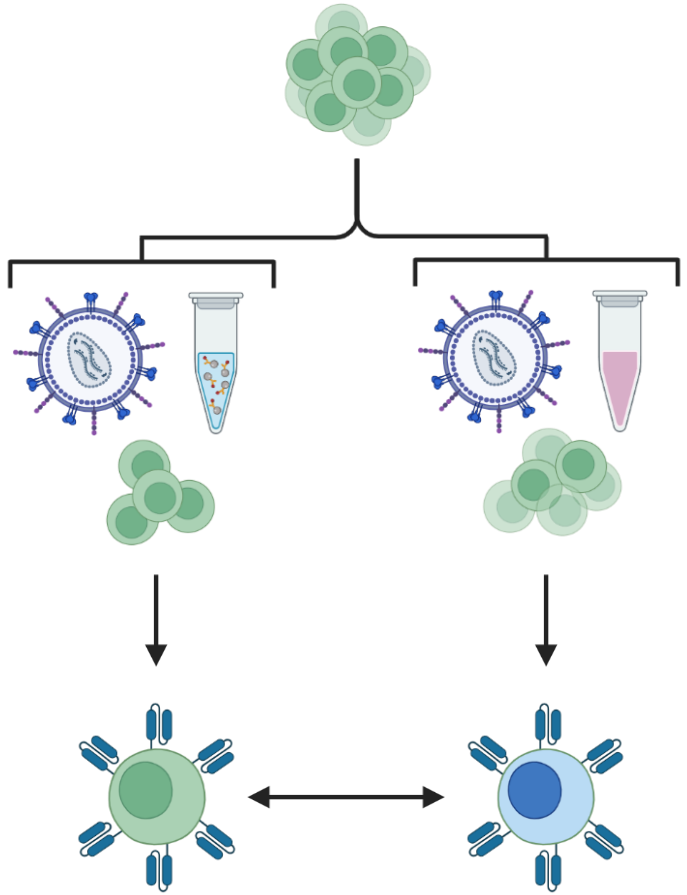
Evaluating comparability – Obtaining FDA input

- Obtaining feedback from the FDA ensures alignment on comparability approach and design.
- Mechanisms to obtain feedback include formal meeting requests, IND amendments, and BLA product correspondence
- Interactions with FDA can be used to:
  - Prospectively discuss significant manufacturing changes
  - Provide detailed comparability protocols for review
  - Align on next steps if products are not comparable

Comparability assessments may necessitate unique study designs

- Many CGTs are impacted by variable starting materials (e.g., autologous products)
- Comparability studies should be designed to address unique considerations for CGTs
- For example, split-study designs can be used to mitigate the impact of starting material variability

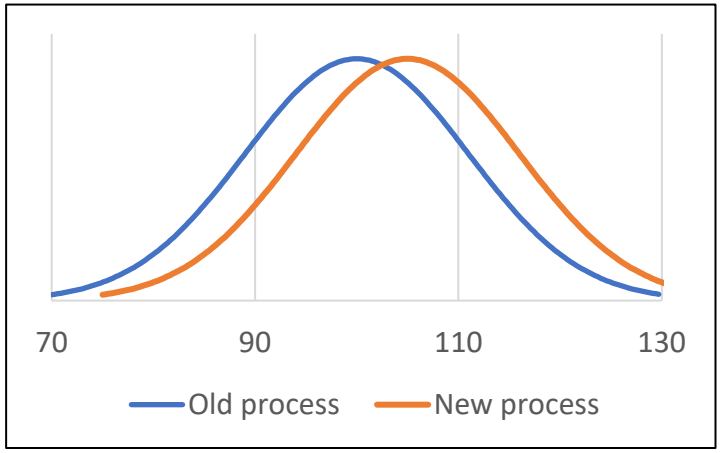
Cell-based products variable starting materials



Evaluating comparability – Statistical considerations

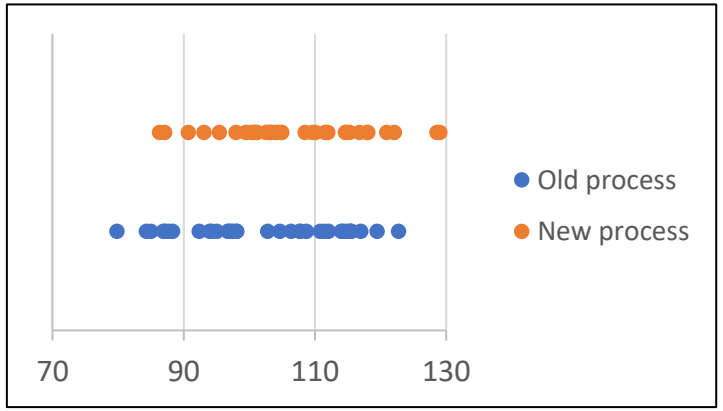
- Similarly, statistical approaches should be chosen based on risk and parameter criticality

Equivalence Testing



Rigorous; high-risk parameters such as dose-determining assays

Quality Range



Less rigorous; suitable for certain Parameters such as impurities

Evaluating comparability – Interpretation

- 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 comparability
  - Comparability studies may be inconclusive due to lack of statistical power, imprecise assays, or poor understanding of DP CQAs
- 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 and key takeaways

- Risk management plays a central role in managing manufacturing changes
- Planning for future changes can ease the implementation of manufacturing changes
- FDA can provide advice for managing manufacturing changes in INDs and BLAs
- FDA adopts phase-appropriate expectations for managing manufacturing changes