Cell & Gene Therapy Automation and Comparability

Common Pitfalls and How to Avoid Them

Agenda:

12:00-12:30 p.m. | Registration and Networking

12:30-12:40 p.m. | Opening Remarks and Introductions, Matt Goserud and PROAnalytics presentation

12:40-1:20 p.m. | Automating Cell Therapies, Seth Andrews, PhD

- Why use Automation
- When to Implement Autologous and Allogeneic Scaling Strategies
- Allogeneic CAR-T Case Study

1:20-2:00 p.m. | Regulatory Considerations for Process Automation - Comparability to Bridge Process Changes, Scott Burger, MD

- When is comparability needed? Regulatory requirements and interactions
- Stage-appropriate comparability studies for auto and allo products
- Accommodating analytical capabilities and resources

2:00 - 2:15 p.m. | Refreshments and Networking

2:15 - 2:45 p.m. | Case Scenarios and Roundtable Discussions

2:45 - 3:15 p.m. | Presentations and Open Discussion

3:15 - 3:30 p.m. | Closing, Matt Goserud

Workshop Leaders

Seth Andrews, PhD
Process Engineer/ Supervisor
IMUGENE

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Principal
Advanced Cell & Gene Therapy

Regulatory Considerations for Process Automation: Comparability to Bridge Process Changes

Scott R. Burger, MD

“The Only Constant in Life Is Change”

– Heraclitus

- Manufacturing and analytical changes are inevitable throughout the product lifecycle
  - Improve product quality, manufacturing efficiency, increase product supply, etc.
- But product quality must remain consistent

So…

- “…risk that a manufacturing change may adversely impact product quality should be prospectively assessed under the manufacturer’s quality risk management processes.”

Draft Guidance on CGT Comparability, 2023

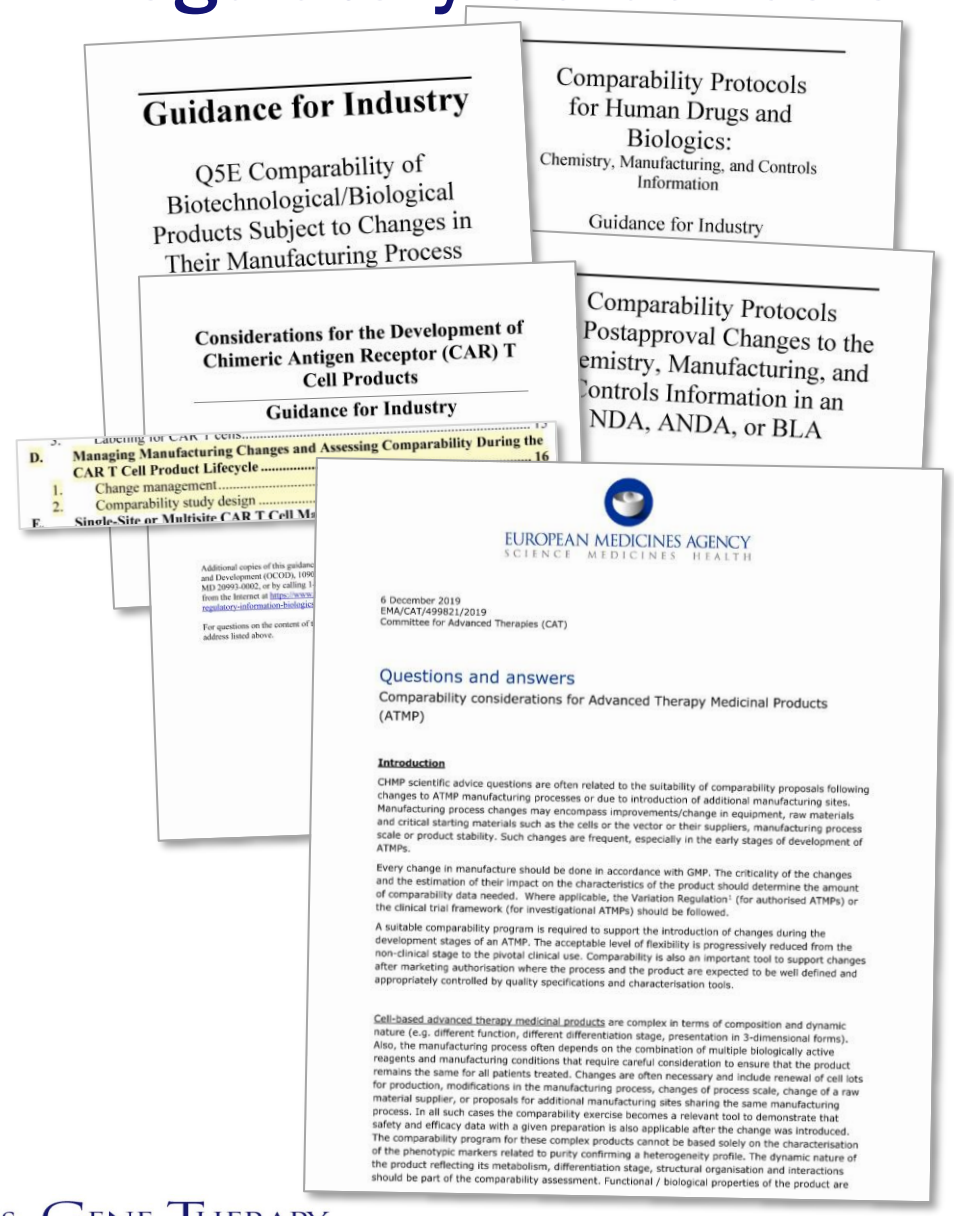
Risk Assessment and Comparability

Perform risk assessment for ***all*** types of manufacturing changes, throughout product lifecycle

If risk assessment indicates potential for adverse effect on product quality, then…

"…**comparability studies** should be performed to evaluate the impact of the proposed manufacturing change."

Regulatory Guidance on 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Draft Guidance for Industry

This guidance document is for comment purposes only.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

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Comparability

- "**Comparability** between the pre-change and post-change products is generally demonstrated by **evidence that the change does not adversely affect product quality…**"

  Draft Guidance on CGT Comparability, 2023

  - "For the purposes of this guidance, the term "**product quality**" refers to **identity, strength, quality, purity, and potency** of a product, as these factors may relate to the **safety or effectiveness** of the product."
  - **Critical Quality Attributes (CQAs)**: "Physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality"

    ICH Q8(R2)

- Comparability does ***not*** mean that pre- and post-change products are identical or indistinguishable

Comparability Studies

- **Analytical assessment (i.e., *in vitro* comparability) recommended** to determine impact of manufacturing change(s) on product quality
  - Studies supported by knowledge of product and manufacturing process, understanding of relationship between *in vitro* testing and safety/efficacy
- **If analytical studies are insufficient**
  - Nonclinical studies, PK/PD studies may help support evaluation of comparability
- Investigational product
  - More extensive comparability needed for later-stage products or changes with greater risk adversely affecting product quality
- Licensed product
  - Must assess effects of "each change in the product, production process, quality controls, equipment, facilities, responsible personnel, or labeling established in the approved license application(s)"

21CFR 601.12(a)(1)-(2)

If Comparability Cannot Be Established

- If comparability has been properly performed, lack of comparability indicates adverse effect of manufacturing change on quality of post-change product. May compromise safety and/or efficacy of post-change product.

- **Investigational product**
  - Data from clinical trials of pre-change product will not be sufficient for BLA of post-change product
  - Need additional clinical studies of post-change product safety and/or efficacy. Discuss plans with FDA.

- **Licensed product**
  - FDA cannot approve the manufacturing change
  - Discuss alternative approaches with FDA, will evaluate on a case-by-case basis.

Risk Assessment of Manufacturing Change(s)

- Assess potential impacts of change on product as well as manufacturing steps and in-process parameters downstream of change
- CGT Comparability Guidance recommends FMEA approach (though not by name)
  - Risk Priority Score = Probability x Severity x Detectability
  - Changes scored as higher risk require more extensive comparability, more stringent statistical analysis
- Factors to consider
  - Product and process knowledge - gaps in knowledge increase risk
  - Nature and magnitude of change(s)
  - Qualification/validation of methods
  - Product and clinical development stage

Example Changes With Risk Potential
Manufacturing site changes
Manufacturing process
Materials
Container closure
Testing
Storage
Shipping conditions

Draft Guidance on CGT Comparability, 2023 (p. 10)

Comparability Study Protocol

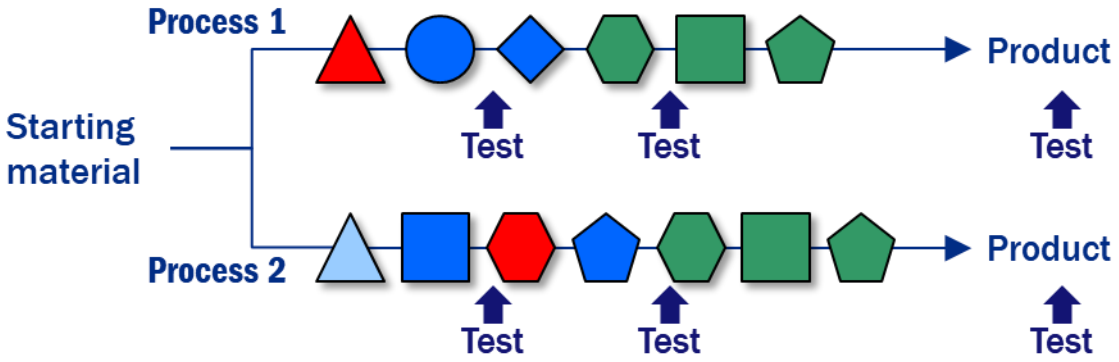
- Based on risk assessment findings
- Comprehensive, prospectively written plan for assessing effect of proposed CMC change(s)
  - Description of planned change(s)
  - Summary of risk assessment
  - Description of study design(s)
    - Quality attributes to be tested, analytical methods
    - Acceptance criteria
  - Statistical methods
- Prior to conducting study, submit a detailed comparability study protocol to FDA, request feedback

Product Lots For Comparability

- If possible, comparability should use lots manufactured at full scale
  - May use lots from scaled-down manufacturing, if justifiable by data-driven risk assessment of CQAs, CPPs, other characteristics
- Can compare pre-change historical data to newer data from post-change lots, if analytical methods are equivalent

Cellular Starting Material and Study Design

- Variability of cellular starting material often presents challenges, particularly for autologous products
- "…use a split-source study design, whenever possible"



  - Paired difference analysis of data
  - Potential for artifact due to reduced number of cells

- Ideally, cellular source material should be the same as normally used in manufacturing, but supply of patient cells may be limited
  - May use cells from healthy donors or perform small-scale manufacturing runs. Include justification in study protocol and report.

Analytical Methods

- **Release testing and in-process controls are *not* sufficient**
  - Test quality attributes not routinely measured, *in addition to* lot release testing and in-process controls
  - **Use additional well-controlled analytical methods**
  - Orthogonal methods increase certainty
    - Evaluate in risk assessment, include in comparability if assessment supports
    - Orthogonal potency measures are invaluable
- Perform testing consistently
  - Side-by-side testing (testing pre- and post-change samples in the same experiment)

    OR
  - Analyze all samples using same analytical method performed at the same testing facility
- Use reference material, if available (in-house standards, retains)

Comparability Acceptance Criteria

- Prior to performing comparability, specify acceptance criterion for each quality attribute to be measured.
- **Meeting release criteria is *not* sufficient to demonstrate comparability**
  - **Release** criteria are as ***broad*** as possible without compromising safety/efficacy
  - **Comparability** acceptance criteria must be ***narrow*** enough to detect meaningful change in product or process intermediate or process
- Determine acceptance criteria based on data prior to manufacturing change
  - "Largest acceptable difference between pre- and post-change attribute (an **equivalence margin**)"

    OR
  - "Acceptable range for the post-change attribute (a **quality range**)"

Potency Assessment

- If possible, analytical methods should include quantitative potency testing
  - If established potency testing lacks precision or does not test all relevant aspects of MOA, may use multiple potency assays, if available
- May supplement potency assay(s) with animal studies, if necessary
- If potency testing has not yet been established, analysis may be performed in future using retain samples
  - One of many reasons to retain samples from all lots

Statistics

- CGT Comparability Guidance includes extensive discussion of potential statistical approaches and their applicability

- "We recommend that you **consult with a statistician before discussing the study design and statistical approach with FDA.** There could be multiple appropriate statistical methods that may be used to evaluate whether data from the post-change product are within predetermined acceptable limits."

FDA Draft Guidance - Manufacturing Changes and Comparability for Human Cellular and Gene Therapy Products, 2023

Communicate with FDA!

- "…seek FDA advice… when **planning** significant manufacturing changes and when **designing** study protocols for comparability studies."
  - Meeting request
  - Request FDA comment on information in an IND amendment or BLA product correspondence

Comparability Study Report

- Evaluation of comparability data, including historical data, determine whether pre- and post-change products are comparable.
  - Results, conclusions and discussion, study limitations
- CTD 3.2.S.2.6 or 3.2.P.2.3 -- Manufacturing Process Development

Regulatory Reporting

- Update CTD Module 3 and other relevant sections to reflect new manufacturing process.
- Update manufacturing process development history in CTD 3.2.S.2.6, 3.2.P.2.3
- Investigational product
  - Submit changes to CMC information as IND amendment(s)
- Licensed product
  - Submit changes as a supplement to BLA or in annual report

Summary

- Comparability across manufacturing changes is based on evidence that the change does not adversely affect product quality. Comparability does not mean that pre- and post-change products are identical or indistinguishable.
- Risk assessment drives comparability studies. Given the complexity of CGT products, a systematic approach is necessary.
- Early in development, gaps in understanding of product CQAs, manufacturing CPPs, and MOA increase risks of manufacturing changes. Lack of analytical methods, particularly for testing potency testing, can hamper comparability studies.
- Communicate with FDA about plans for manufacturing changes and comparability

References and Resources

- FDA Draft Guidance - Manufacturing Changes and Comparability for Human Cellular and Gene Therapy Products, 2023
- FDA Draft Guidance - Considerations for the Development of Chimeric Antigen Receptor (CAR) T Cell Products, 2022
- ICH Q9(R1) - Quality Risk Management
- FDA Guidance - CMC Information for Human Gene Therapy INDs, 2020
- BSI PAS 83 - Developing human cells for clinical applications in the European Union and the United States of America, 2012
- ICH Q5E - Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process, 2005
- FDA Draft Guidance - Comparability Protocols for Human Drugs and Biologics: CMC Information, 2016
- FDA Guidance - Comparability Protocols for Postapproval Changes to the Chemistry, Manufacturing, and Controls Information in an NDA, ANDA, or BLA, 2022