

Adapting the Principles of Comparability for Complex ATMPs

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ICH Q5E Provides the Principles for Comparability



Issued 2005

Guidance for Industry

Q5E Comparability of
Biotechnological/Biological
Products Subject to Changes in
Their Manufacturing Process

Purpose of Comparability Exercise

Ensure there is no adverse effect of changed manufacturing process on quality, safety, and efficacy of drug product – ICH Q5E

Support CONTINUITY throughout the lifecycle of product

- From preclinical to FIH (representative batches)
- through all stages of clinical development
- marketing application (efficacy)
- post-approval

ICH Q5E: Comparable does not require Identical



The demonstration of comparability **does not necessarily mean that the quality attributes of the prechange and postchange product are *identical***, but that they are highly similar and that existing knowledge is sufficiently predictive to ensure that any differences in quality attributes have no adverse impact upon safety or efficacy of the drug product.

Improvements in product quality are encouraged with proper supportive information.



Scope of ICH Q5E

- **Proteins and polypeptides, their derivatives, and products of which they are components**, e.g., conjugates. These proteins and polypeptides are produced from recombinant or non-recombinant cell-culture expression systems and can be highly purified and characterized using an appropriate set of analytical procedures;
- **Products where manufacturing process changes are made by a single manufacturer**, including those made by a contract manufacturer, who can directly compare results from the analysis of prechange and postchange product; and
- Products where manufacturing process changes are made in development or for which a marketing authorization has been granted.
- The principles outlined may also apply to other product types.

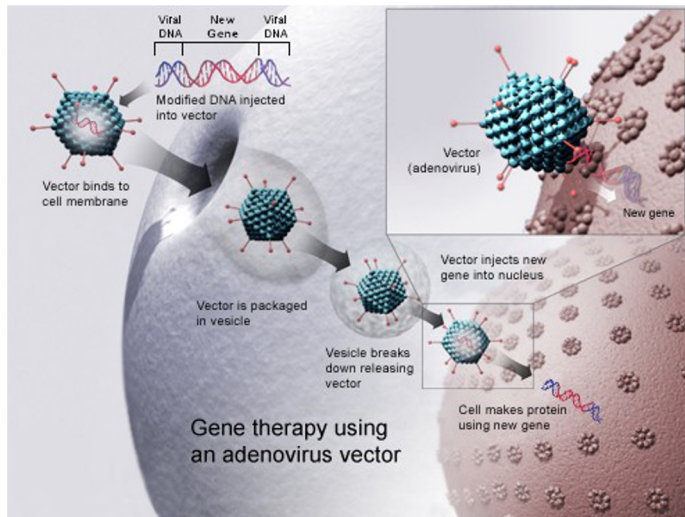
Sound principles for assessing comparability are provided in Q5E but may be difficult to strictly apply to ATMPs

ATMPs are broad range of products and complexity

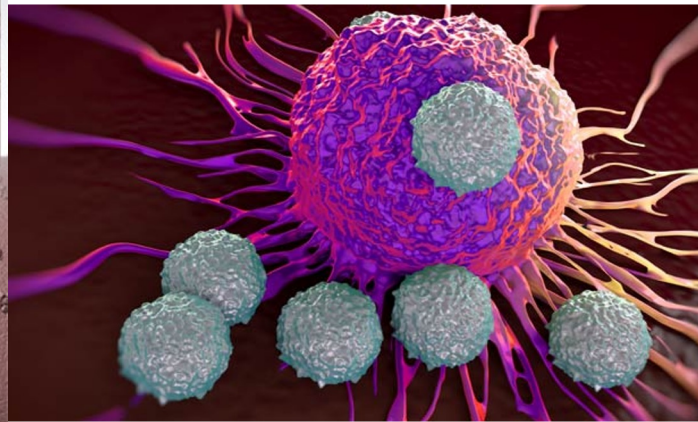
Advanced therapy medicinal products (ATMPs) are innovative therapeutics that encompass gene therapy, somatic cell therapy, and tissue-engineered products.

Wide range of complexity

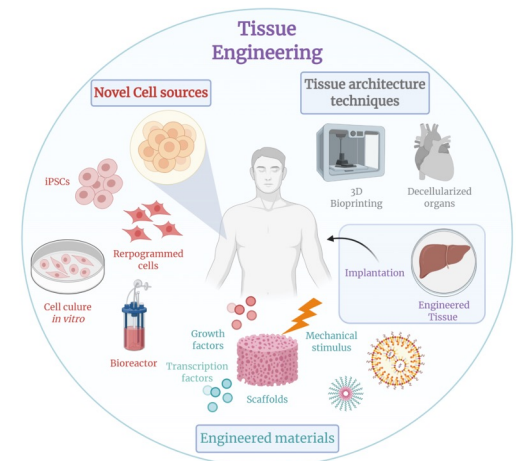
Gene therapy Product



Cell therapy products



Tissue Engineered products



ATMPs are out of scope of ICH Q5E

Current Regulatory Guidelines that address ATMP Comparability

- EMA: Questions and answers on comparability considerations for advanced therapy medicinal products (ATMP), 2019
- FDA/CBER: Manufacturing changes and comparability for human cellular and gene therapy products (draft), 2023
- MHLW/PMDA: Guideline for comparability of human cell-processed products subject to changes in their manufacturing process, 2024
- NMPA: Technical guidelines for the study and evaluation of CMC changes in cell therapy medicinal products (draft), 2025

Future Guidance: ATMP Annex to ICH Q5E



New ICH Topic Proposal Endorsed by ICH Assembly, May 2025

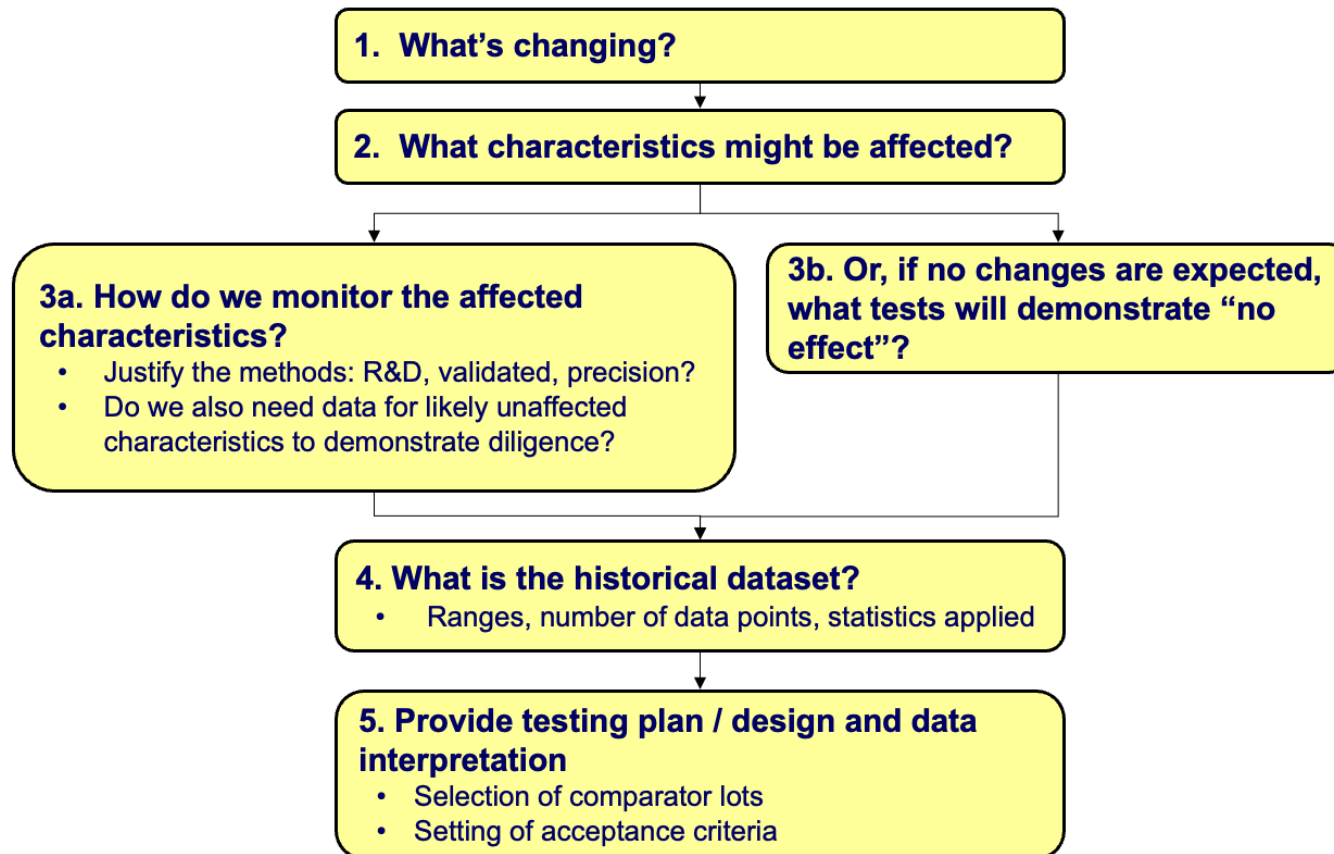
Comparability of Advanced Therapy Medicinal Products (ATMPs) Subject to Changes in Their Manufacturing Process (Annex to ICH Q5E)

- *ICH web site: Press release (21 May 2025) ICH Assembly Meeting, Madrid, Spain*
- A new Annex to the ICH Multidisciplinary Guideline ICH Q5E is proposed to address the unique development and regulatory challenges of ATMPs, such as gene and cell therapies.
 - Recommendation from **ICH Cell & Gene Therapy Discussion Group** (CGTDG)
 - Sponsor BIO (Biotechnology Innovation Organization)

Many reasons for manufacturing changes, including ...

- Change of manufacturing site
 - Scale up or *out*
- Manufacturing process improvement (e.g., increase yield)
- Change of raw material
- Improve product stability
- Improve product purity
- Comply with changes in regulatory requirements
- *Reduce production cost*

The approach to comparability is logical



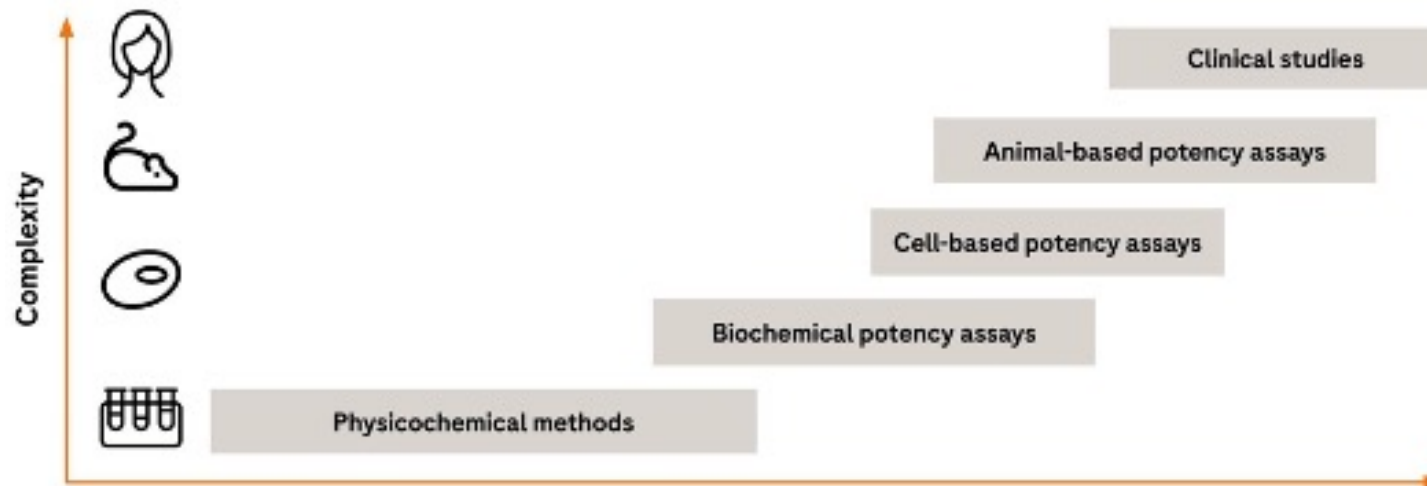
- Consider what questions to ask
- Risk-based approaches
- Cannot use same approach for all ATMPs uniformly
- Fit-for-purpose

Comparability exercises can include nonclinical and/or clinical studies in addition to analytical testing

ICH Q5E: “A determination of comparability can be based on a combination of analytical testing, biological assays, and, in some cases, nonclinical and clinical data.

If a manufacturer can provide assurance of comparability through analytical studies alone, nonclinical or clinical studies with the postchange product are not warranted.

However, where the relationship between specific quality attributes and safety and efficacy has not been established, and differences between quality attributes of the pre- and postchange product are observed, it might be appropriate to include a combination of quality, nonclinical, and/or clinical studies in the comparability exercise.”



Comparability considerations for ATMPs

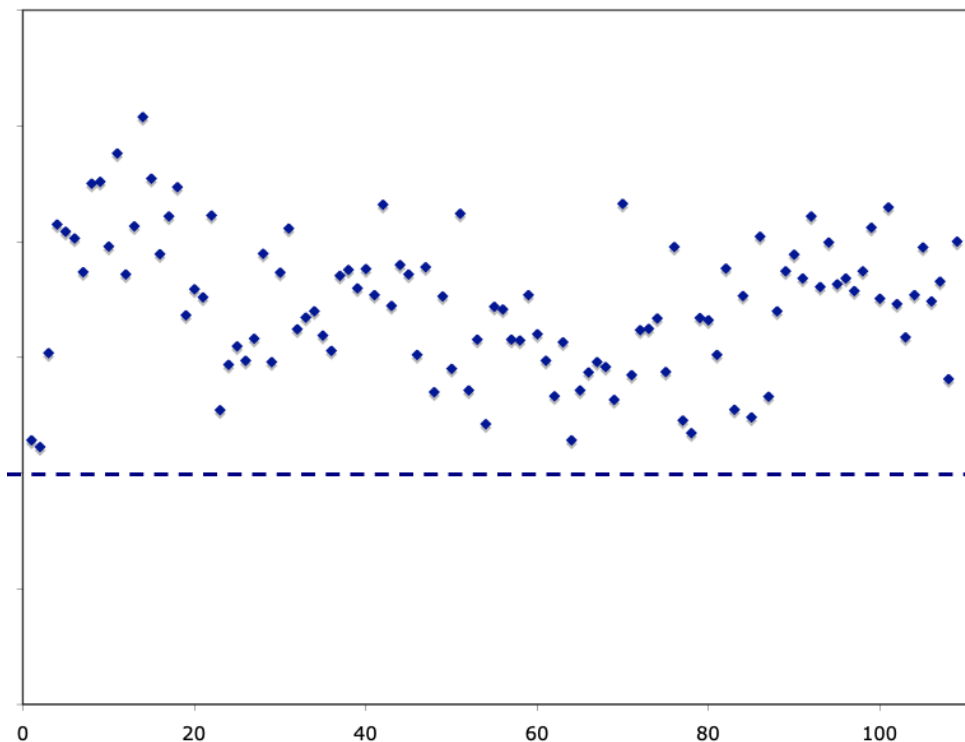
- Limited amounts of product – scarcity constrains many aspects
 - Small batch sizes (e.g. for autologous products)
 - Few batches for rare disease medicines (e.g. 1-2 batches)
- Product complexity and variability
 - Virus particles; Cells; Tissues
 - Inherent variability of cellular starting materials – and final product
- Patient-specific products (i.e. individualized) have constant elements and patient-specific elements of the product
 - Autologous cell-based products
 - *In vivo* genome editing products
- Incoming materials are often human or animal derived
 - Complex and may not be well defined
 - Batch to batch variability of materials
 - Inherent patient-to-patient or donor-to-donor variability

Limited Amount of ATMP Product

- CGT products are often produced in small amounts
 - For autologous cell-based products, starting cells are from patient
- Production may be complex, manual, patient-specific
- There are often only small amounts of material available for:
 - development of analytical techniques
 - characterization studies
 - release testing
 - stability testing
 - comparison of pre- and post-change products
 - nonclinical studies
 - clinical studies
- **Approach taken must accommodate both product *and* patient needs.**

Number of manufactured batches

Depends on ATMP product and disease indication



One batch per patient for individualized ATMPs:

- Autologous cell-based products
- *In vivo* genome editing products

Few batches (e.g. 2) for entire clinical program for viral vector-based gene therapy for rare disease

- Challenge to demonstrate manufacturing consistency
- Statistical analyses may not be feasible

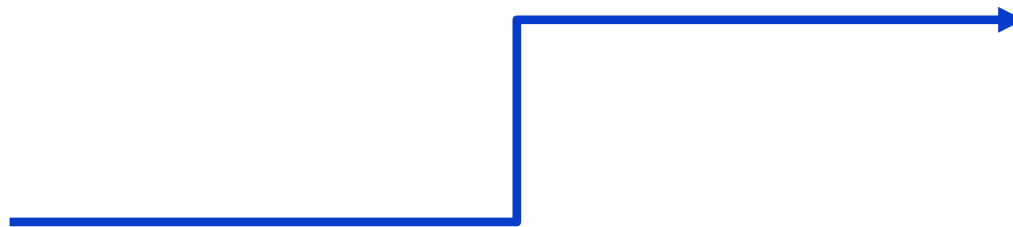
Analytical Method Limitations

- Analytical methods supporting CGT products are often product-specific, unconventional, and complex.
 - Early implementation of reference materials, assay controls is recommended to enable bridging to new and improved analytical assays
- Side-by-side testing of complex ATMPs in same analytical run can help reduce the sources of variability

Product understanding:

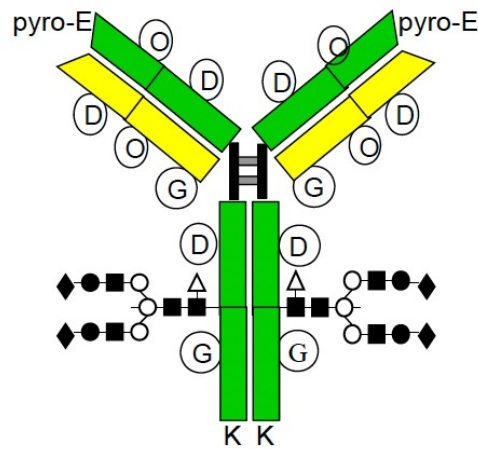
Early development of analytical characterization tools is needed.

→ Taking into account the variability, both intended and unintended, of incoming materials and of the product itself.



**Comparability assessments become challenging
for cell- and tissue-based products**

Mabs are well characterized at molecular level...



Total variants
(9600)² ≈ 10⁸

Pyro-Glu (2)

Deamidation (3 x 2)

Methionine oxidation
(2 x 2)

Glycation (2 x 2)

High mannose, G0,
G1, G1, G2 (5)

Sialylation (5)

C-term Lys (2)

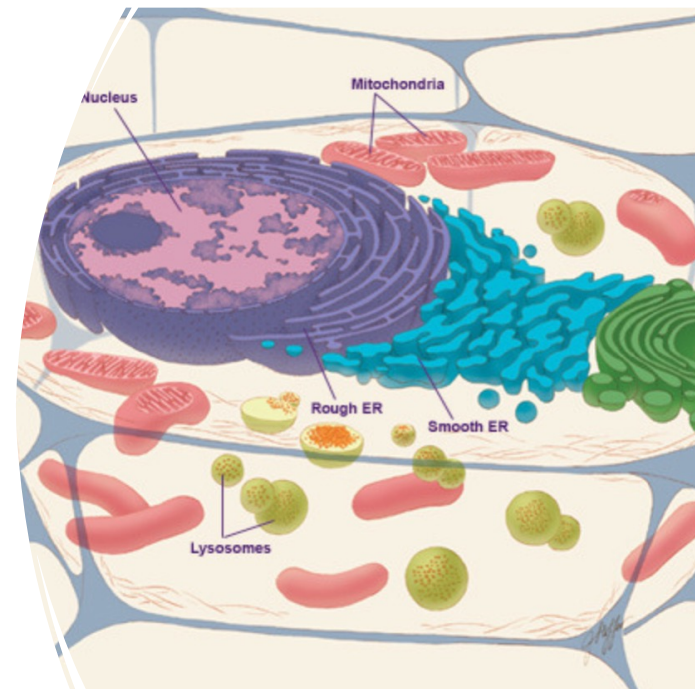
$$2 \times 6 \times 4 \times 4 \times 5 \times 5 \times 2 = 9600$$

- Analytical methods to characterize recombinant protein products, e.g., HPLC (SEC, IEC), CE, mass spectrometry, etc.
- Studies to understand the role of the quality attributes (e.g. in clearance, PK, bioactivity) ... or perhaps no obvious impact

In contrast to small and large molecules, it is quite difficult to characterize cells at molecular level



- Cells are highly complex, heterogeneous, and dynamic
- Metabolism, cell signaling, cell cycle, differentiation, apoptosis, migration, viability; etc.
- Heterogeneity of cell population



Few techniques currently available to evaluate cell health status, functionality, etc.

Limited characterization and understanding of cell-based products, currently.

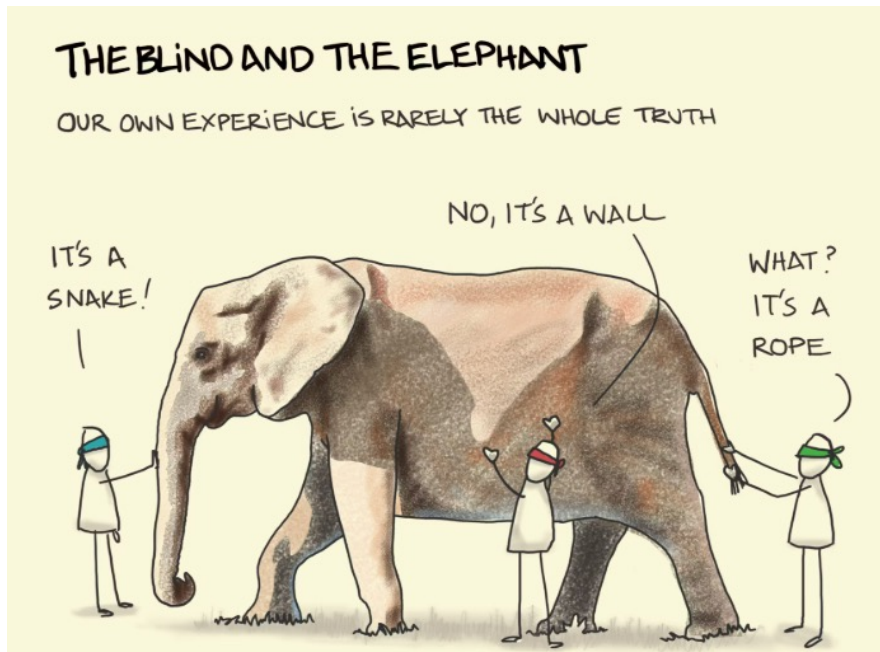


Parable of the blind and the elephant:

Limited perspectives lead to conflicting conclusions about the same thing

Each blind man touches a different part of the elephant (e.g. trunk, side, tail) and concludes it is something else (e.g., snake, wall, rope).

They argue with one another, failing to see the larger picture until a wise person explains that all their descriptions are correct, but only describe a small part of the whole.



Totality of evidence is crucial for assessing comparability of cell- and tissue-based ATMPs

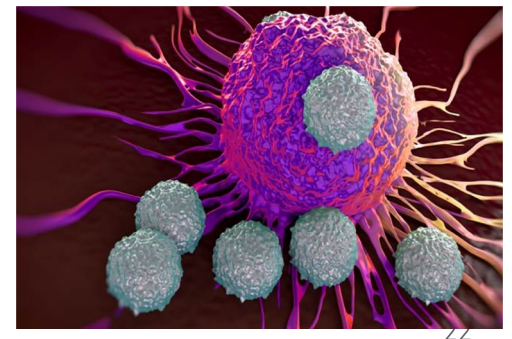
- Comprehensive assessments may involve:
 - Product quality – current ability to detect product quality attributes; limited product understanding; continue to develop analytical techniques for characterisation
 - Impact of incoming materials (raw materials, starting materials)
 - Manufacturing process comparisons
 - Possible nonclinical and/or clinical data.
- Incremental, stepwise implementation of CMC changes more likely to support continuity of ATMP lifecycle
- Statistical analyses may not be feasible or meaningful
 - cell-based and tissue-based ATMPs
 - rare disease products with very few batches or even “Nof1”

Impact of Incoming Materials

- Raw materials can have significant effect upon final ATMP
 - Quality and consistency of raw materials are particularly important for cellular therapies– cells tend to be sensitive to minor variations
 - Introduction of new raw material batches from same vendor, or raw materials from new vendors, should be evaluated carefully
 - Comparability assessments focused at level of materials
- Cellular starting materials are inherently variable, but not well understood
 - Variability from patient to patient for autologous products
 - Variability from donor to donor for allogeneic products
 - Use of **surrogate starting cells** (e.g., from healthy donors) may be needed for comparability assessment of autologous products provided they are representative

Manufacturing process can play a large role in defining cell-based products

- When ATMP is complex and not well defined, and manufacturing process largely defines the product, then comparison of manufacturing processes should be substantial part of total data package
- Focus comparability assessment on process steps where change is implemented.
- Incremental improvements in process may be more manageable



Split Manufacturing can be effective when assessing comparability of individualized products

- Manufacturing stream is split at point of the change and run in parallel downstream
- Can be used effectively for individualized (i.e., patient-specific) products:
 - new manufacturing sites
 - process improvements/changes
- Use same batches of raw materials to reduce batch-to-batch variability, when feasible
- Head-to-head comparisons (e.g., on resulting pairs of DS or DP batches).

Francissen, K., Chang, A., Donigan, K.A., Hernandez, E.C., Gunter, S. (2023) Comparability Considerations for Cellular & Gene Therapy Products, *Pharmaceutical Engineering* (2023)

Non-clinical and/or clinical data may be needed

For ATMPs, product quality data package may be limited, so non-clinical and/or clinical data may be needed to determine whether there has been an adverse effect on product quality, safety, or efficacy

While non-clinical data may be desirable to assess the potential impact of manufacturing changes on product quality, safety or efficacy, there may not be good animal models for CGT products.

If animal studies are conducted, their relevance to patients should be considered.

There may also be limitations in the sensitivity of in vivo assessments to changes in product quality.

TOTALITY OF EVIDENCE

Doing now what patients need next



Personalized medicine

Finding the right drug on the shelf to treat the patient

versus

Individualized medicine

Creating the right drug to treat the patient