The Only Constant In Life Is Change: Managing Process Changes to Speed Innovation for the Commercialization of ATMPs

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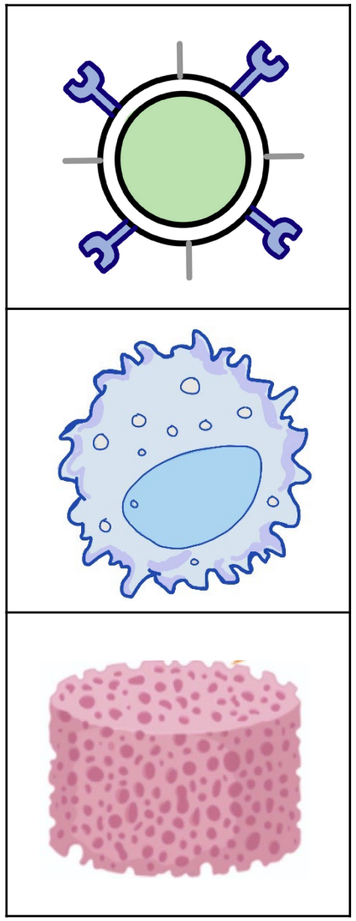
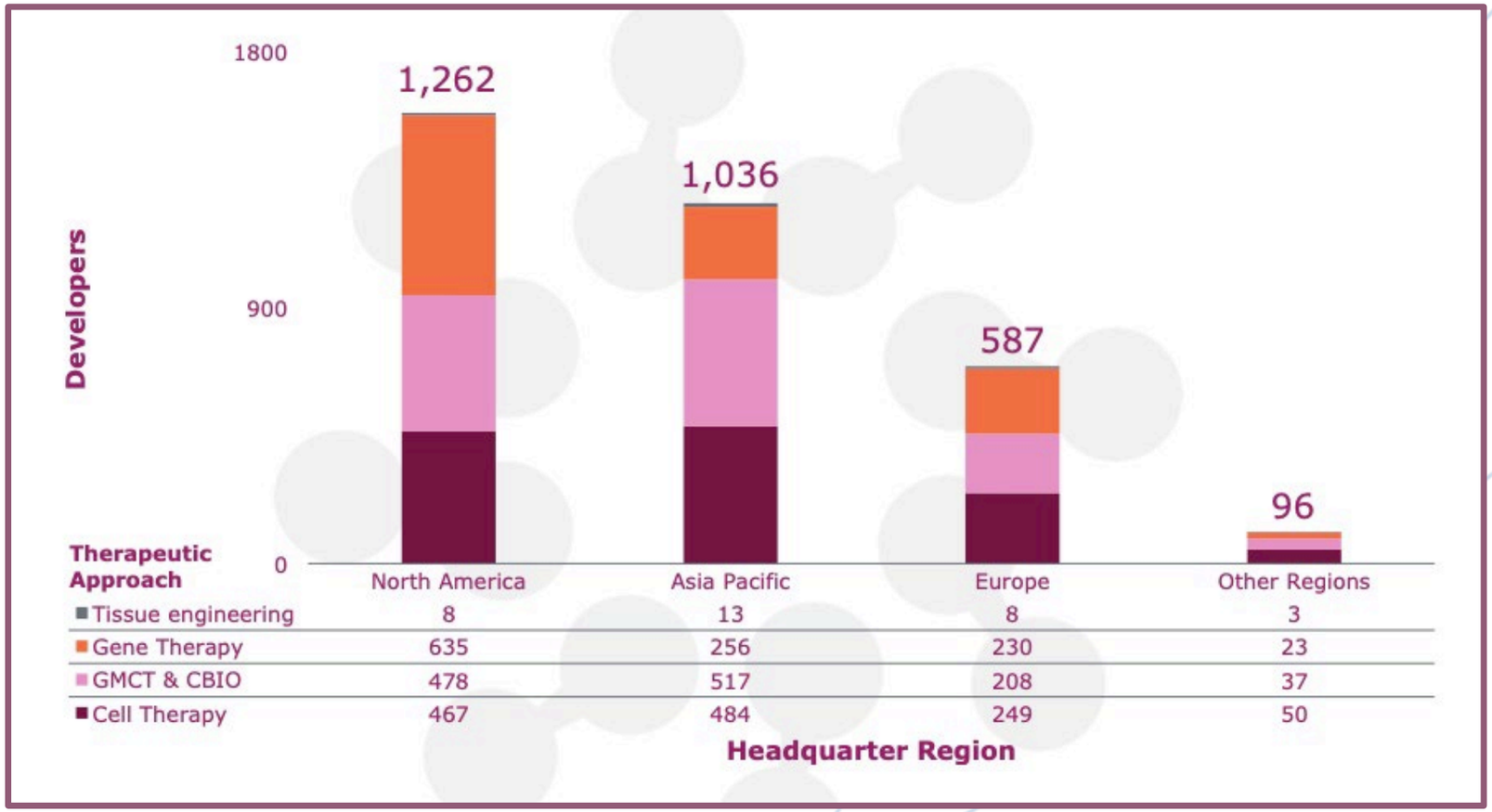
The Current ATMP Landscape

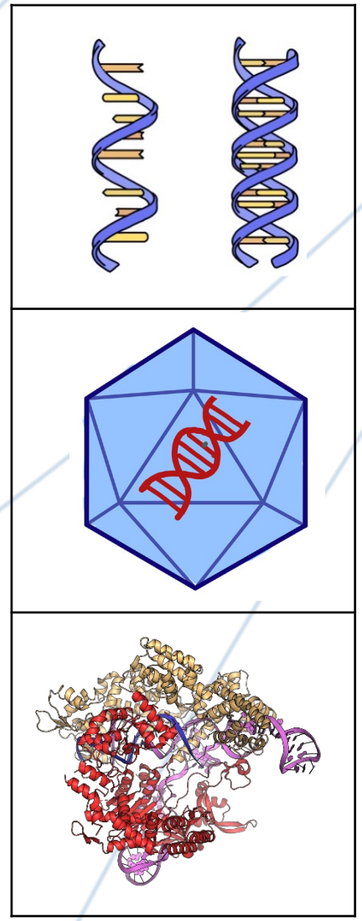
"We may not believe in miracles. But there are things that are miraculous, and this is one." — Peter Marks

(in reference to Zolgensma gene therapy for treatment of SMA type 1)





Therapeutic Approach	North America	Asia Pacific	Europe	Other Regions
Tissue engineering	8	13	8	3
Gene Therapy	635	256	230	23
GMCT & CBIO	478	517	208	37
Cell Therapy	467	484	249	50

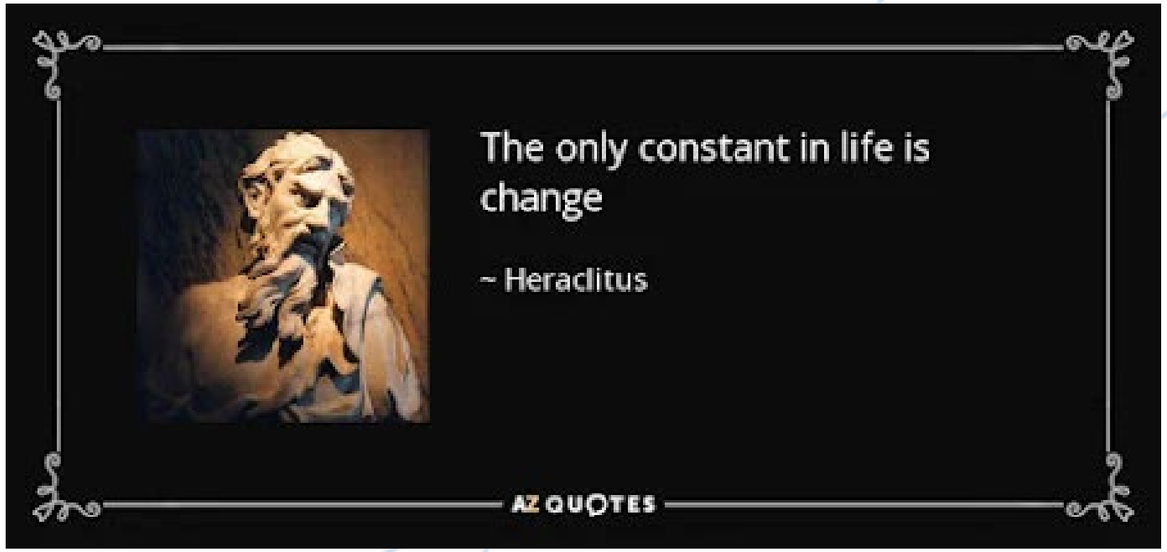


FOR MORE ON THIS TOPIC : https://alliancerm.org/wp-content/uploads/2025/01/20250107-2024-Sector-Snapshot.pdf

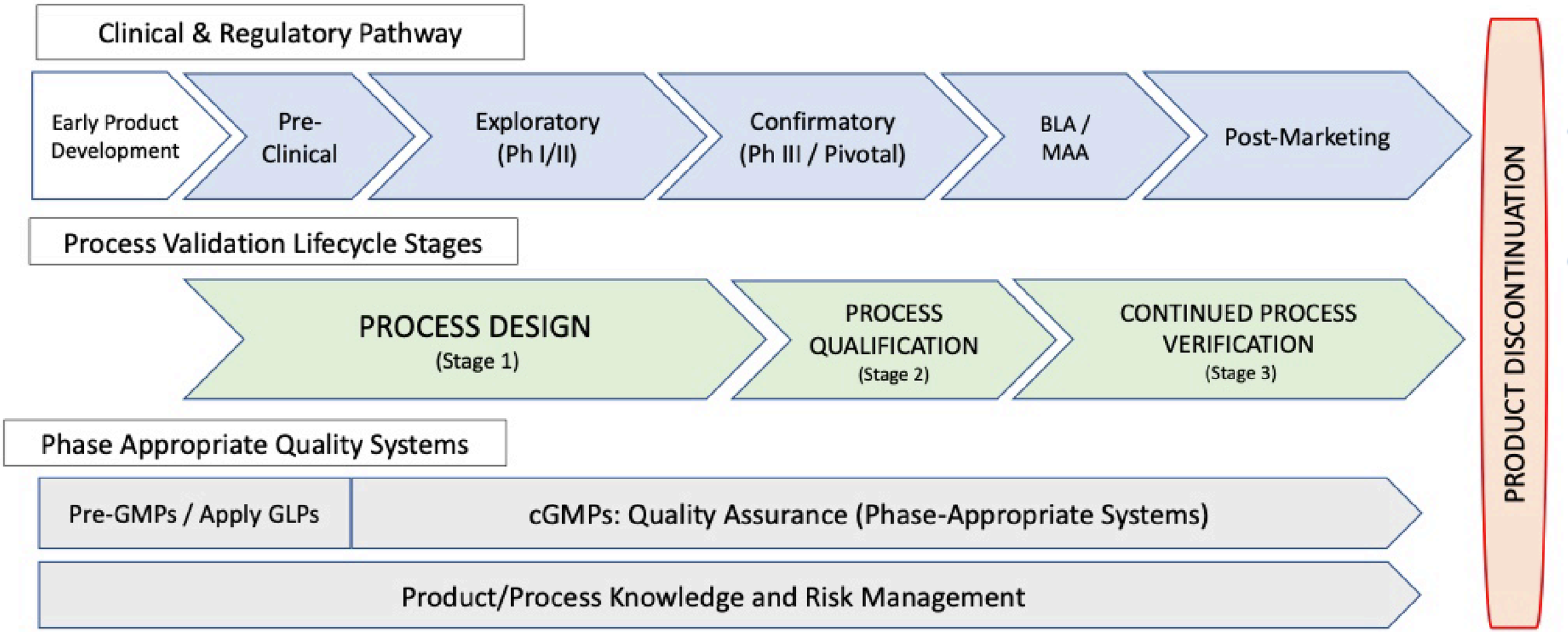
Presentation overview

Topics for our Discussion This Evening …

- The Path to Commercialization: Accelerating Product Development
- Embracing Change and How it Supports Speed to Market for ATMPs
- The Unique Challenges with Managing Process Changes for ATMPs
- Risk-based Approach to the Design of the Product Comparability Study to Support Process Changes



The Path to Commercialization



Evolving Global Regulations for ATMPs

An Evolving Global Regulatory Landscape

Communication with the Health Authorities is critical to accelerating product development...

- Office of Therapeutic Products (part of CBER) - cGMPs regulations apply to Cellular and Gene Based Therapies (43 approved)
- cGMP regulations supplemented by multiple specific guidance documents released and in draft (and available for comment)

Accelerated Pathways to Commercialize ATMPs

- OTP INTERACT meetings
- RMAT designation by FDA and PRIME by EMA

FOR MORE ON THIS: FDA cell and gene therapy guidance https://www.fda.gov/vaccines-blood-biologics/biologics-guidances/cellular-gene-therapy-guidances

The Path to Commercialization

The Only Constant in Life is Change...

*What is **Change**?*

- Change (verb): is to make or become different [per the Cambridge dictionary]
- Many types of change: developmental, transitional, transformational

*Why **Change**?*

- *Innovation and continual improvement – to provide products that consistently meet product quality (safe and efficacious) for patients*

*Why can **Change** be so difficult?*

- The challenge with change comes from our tendency to see changes as problems rather than opportunities for learning and growth.
- Fear of change! Metathesiophobia (actual clinical condition)

FOR MORE ON THIS: **Change: How Organizations Achieve Hard-to-Imagine Results in Uncertain and Volatile Times by John P. Kotter et.al.**

The Path to Commercialization

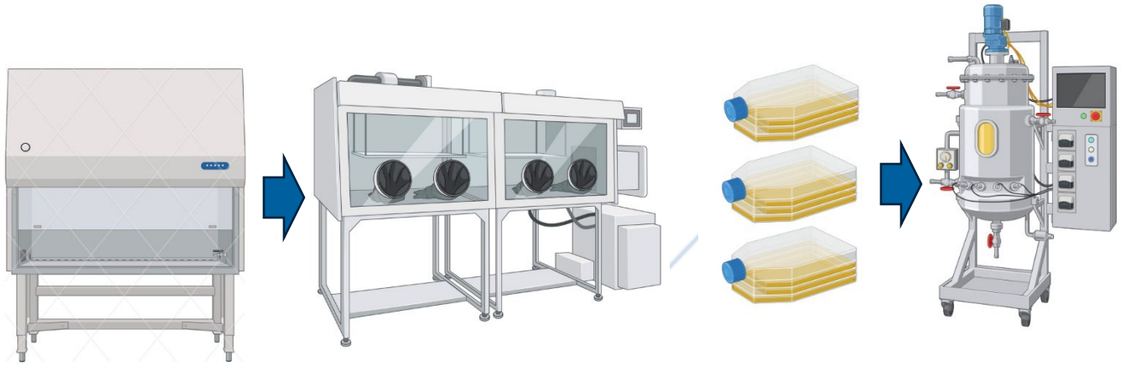
Managing Change is Key to Accelerating Product Development

- The appropriate management of change will support product development and maintain an accelerated timeline to commercialization!
- What can happen if Change is not managed properly?
  - Costly and timely delays to product development
  - Clinical hold or need for additional (needless?) clinical study
  - Harmful impact to the safety of the patient
- Not all changes are the same: the activities performed to support a process change are commensurate with:
  - The impact (criticality) to impact product quality!
  - The stage of the product lifecycle (utilizing a phase-appropriate approach)

Illustrations created with Biorender.com

The Path to Commercialization

Changes to Manufacturing Processes for ATMPs



Illustrations created with Biorender.com

Type of Change	Examples Different ATMPs
Open to Closed (“functionally closed”) aseptic processing	• Initial ‘academic’ process with open, manual steps in a BioSafety Cabinet change to a closed Isolator / RABS for automated fill / finish
New or modified unit operation(s)	• Cell culture system for growth of HEK293 cells to produce AAV viral vector; • Process controls optimized to automated system for the cell selection and activation of a CAR T product
Critical material change to GMP-compliant supply manufacturer	• Non-GMP compliant plasmids supplier to a GMP manufactured supplier to manufacture the viral vector for a gene-modified cell therapy
Early clinical site of manufacture to the proposed commercial site	• Decentralized / Scale-out of a cellular-based therapy in anticipation of expanded commercial supply

The Path to Commercialization

Managing Change is Key to Accelerating Product Development

Types of Manufacturing Changes	Reason(s) for the Change	Examples of Activities To Support the Change
New or modified unit operation(s)	• Consistent quality & process performance • Eliminate or reduce high levels of a residual process impurity (also may introduce new impurities)	• Process risk assessments • Process development and/or characterization studies • *Product Comparability Study* • Process Performance Qualification (PPQ)
Manual to automated (semi-automated) processing	• Improve process controls • Mitigate high aseptic risks associated with manual processing • Consistent process performance	• Process and equipment risk assessments • Equipment qualification • Aseptic Process Simulation (APS) • *Product Comparability Study*
New components / materials (ancillary, excipients, starting)	• Optimize process to reduce aseptic risks • Additional suppliers to reduce supply chain risks • Change from research grade to cGMP grade	• Aseptic risk assessment • Aseptic process simulation (APS) • *Product Comparability Study* • Extractables & Leachables risk assessment
New Site of Product Manufacture (e.g., Decentralized mfg)	• Increase capacity • Provide internal or external manufacturing capabilities • cGMP certified site for later clinical stage and/or commercial manufacturing	• Process and facility risk assessments • Technology Transfer • Facility/Equipment/Utilities qualification and validation • *Product Comparability Study* • Process Performance Qualification (PPQ)

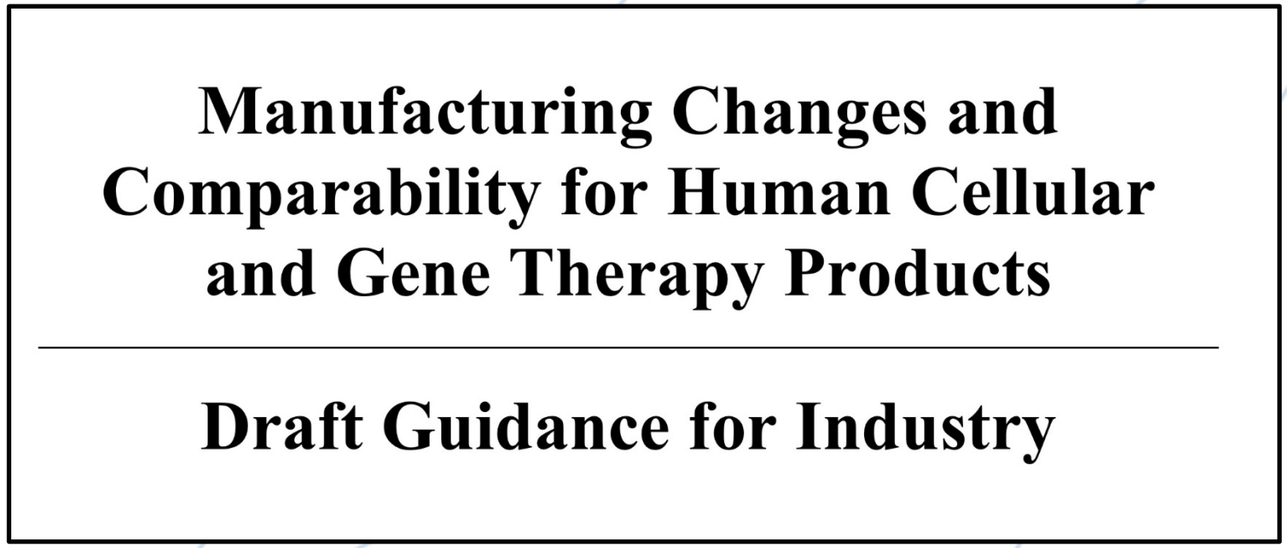
Managing Process Changes

Change Management

Change Management: a systematic approach to proposing, evaluating, approving, implementing and reviewing changes. Goals of innovation and continual improvement. (refer to ICH Q10) and to ensure safe and effective products

FDA Draft Guidance (July 2023) provides current thinking on:

- Management and reporting of manufacturing changes for C&GTs
- Comparability studies to assess the impact of changes on the product and process



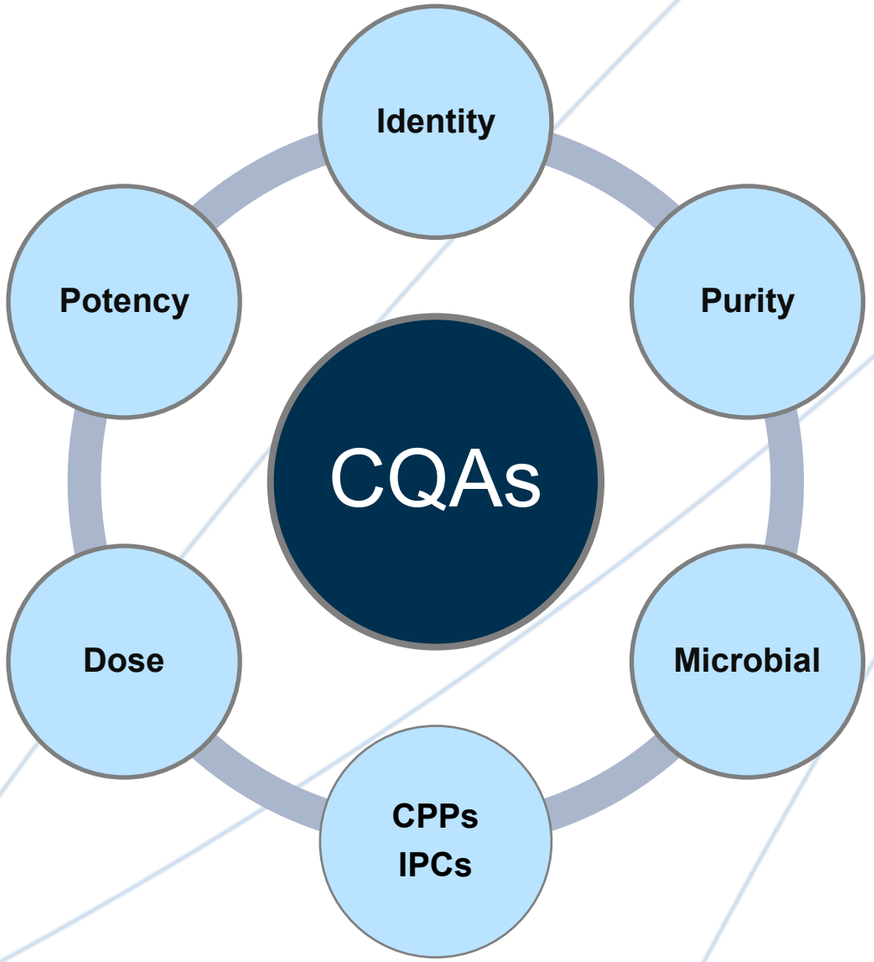
FOR MORE ON THIS: Draft Guidance FDA Docket including all review comments at
https://www.regulations.gov/docket/FDA-2023-D-2436

Managing Process Changes

Product Comparability Study

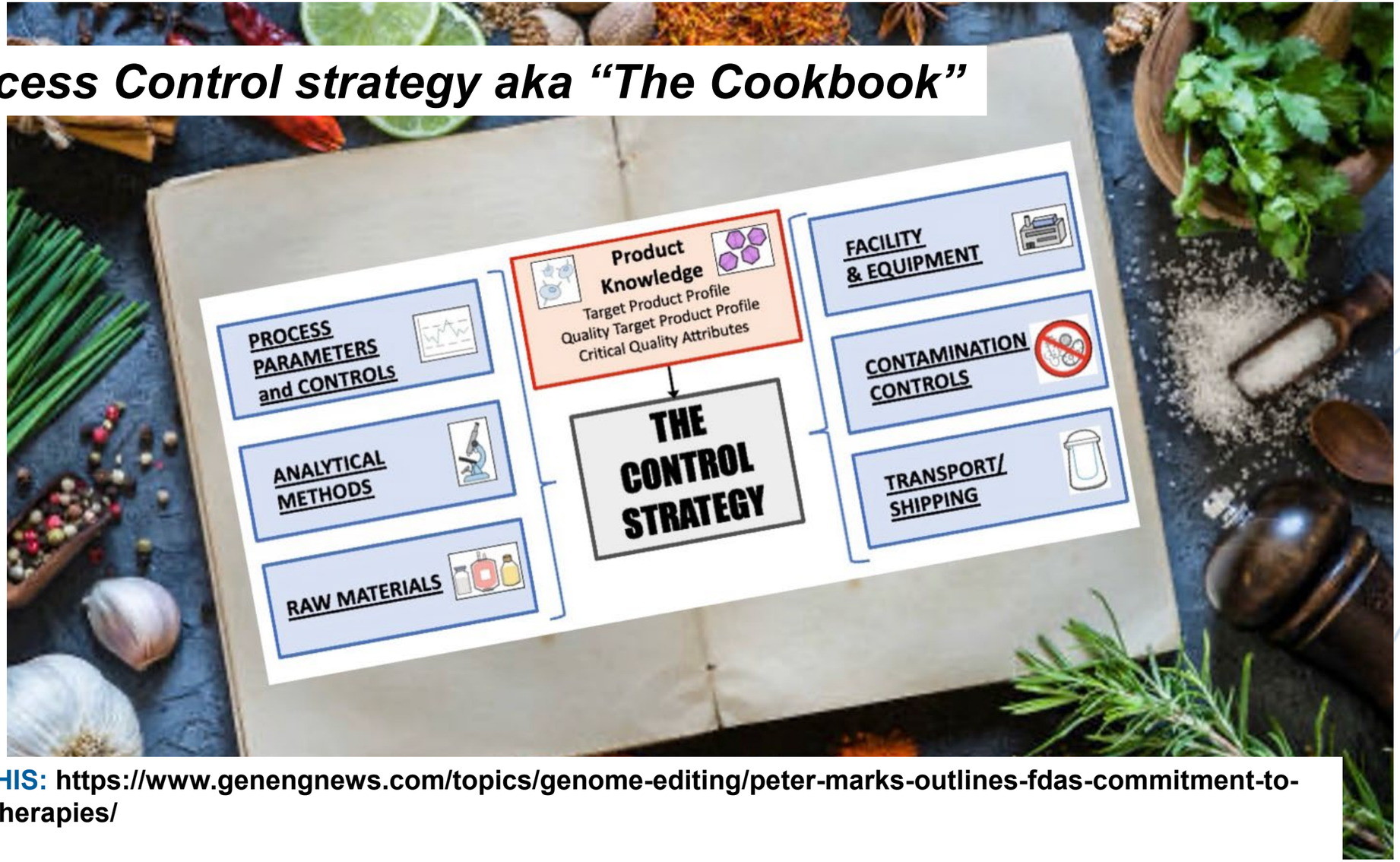
Assess impact of the proposed change on product quality utilizing a risk-based approach (per ICH Q9) taking into account all relevant product knowledge and process understanding.

”…to evaluate whether the proposed manufacturing change may impact product quality, you should conduct a detailed risk assessment as recommended in ICH Q9” (per Draft Guidance)



Managing Process Changes

The Process Control strategy aka "The Cookbook"



FOR MORE ON THIS: **https://www.genengnews.com/topics/genome-editing/peter-marks-outlines-fdas-commitment-to-advancing-gene-therapies/**

A Risk-Based Approach to Change

The Risk Assessment Tool

THE RISK QUESTION:
What is the potential impact of the manufacturing process change on product quality and process performance (i.e., impact to the Control Strategy)??????

SEVERITY →

Impact (Severity)	Description
HIGH	Significant impact to a product CQA (e.g., quality, safety, effectiveness) or to process performance (e.g., product yield)
MEDIUM	Moderate impact to a product CQA (e.g., quality, safety, effectiveness) or to process performance (e.g., product yield)
LOW	Negligible impact to a product CQA (e.g., quality, safety, effectiveness) or to process performance (e.g., product yield)

OCCURRENCE (Likelihood) →

Occurrence	Description
HIGH	Process change expected to significantly impact the variability of the product CQA and/or process performance
MEDIUM	Process change expected to have a slight to moderate impact on the variability of the product CQA and/or process performance
LOW	Process change is not expected to have an impact on the product CQA and/or process performance

Risk-Based Approach to Change

The Risk Assessment Tool

Overall Risk = Severity x Occurrence

Overall Risk		Occurrence		
		LOW	MEDIUM	HIGH
Severity	HIGH	**MEDIUM**	**HIGH**	**HIGH**
	MEDIUM	**LOW**	**MEDIUM**	**HIGH**
	LOW	**LOW**	**LOW**	**MEDIUM**

And what does that **Overall Risk** score mean for the design of the Comparability Exercise?

Acceptance criteria that are "adequate to demonstrate a **lack of adverse effect** of the manufacturing change on product quality"

Overall Risk Ranking	Impact to Design of the Comparability
HIGH	Significant (major) impact to the product CQAs and/or process performance thus requiring assurance in meeting the corresponding acceptance criteria (using Equivalence approach)
MEDIUM	Moderate level of impact based on the change to the manufacturing process. At a minimum, the process variable must be measured and compared to its corresponding acceptable range (Quality Range).
LOW	Negligible impact to product quality and/or process performance thus explicit analysis not required.

Risk-Based Approach to Change

The Risk Assessment Tool

The Output from the Risk Assessment (Example)

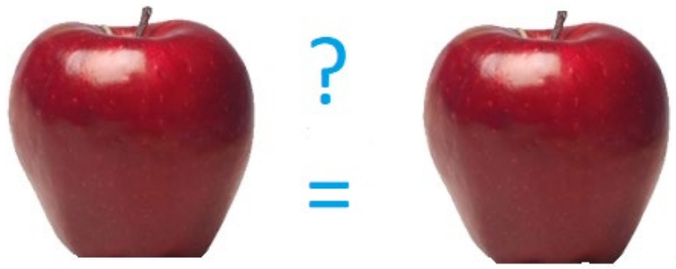
Description of Change	Product Quality and Process Performance Impact								Recommended to Evaluate Product and Process Comparability
	CQA1: Safety	CQA2: Identity	CQA3: Dose	CQA4: Potency	CQA5: Impurity	CQA6: Impurity	PPI1: Growth rate	PPI2: Cell recovery	
Modification to unit operations and process controls									Comparability Required! (Equivalence approach)
Change to Critical Raw Material									Comparability Recommended (Quality approach)
Change to Aseptic Operation									Does not require comparability; Risk to sterility assurance to be evaluated in APS

Risk-Based Approach to Change

The Product Comparability Study

The goal of the comparability exercise is to ensure the quality, safety, and efficacy of drug product produced by a changed manufacturing process, through collection and evaluation of the relevant data to determine whether there might be any adverse impact on the drug product due to the manufacturing process changes. (ICH Q9)

"It is not necessary for the measurements of pre- and post-change CQAs to be identical to reach a conclusion of comparability if there is evidence demonstrating that there is no adverse impact of the change on product quality." (FDA Draft Guidance)



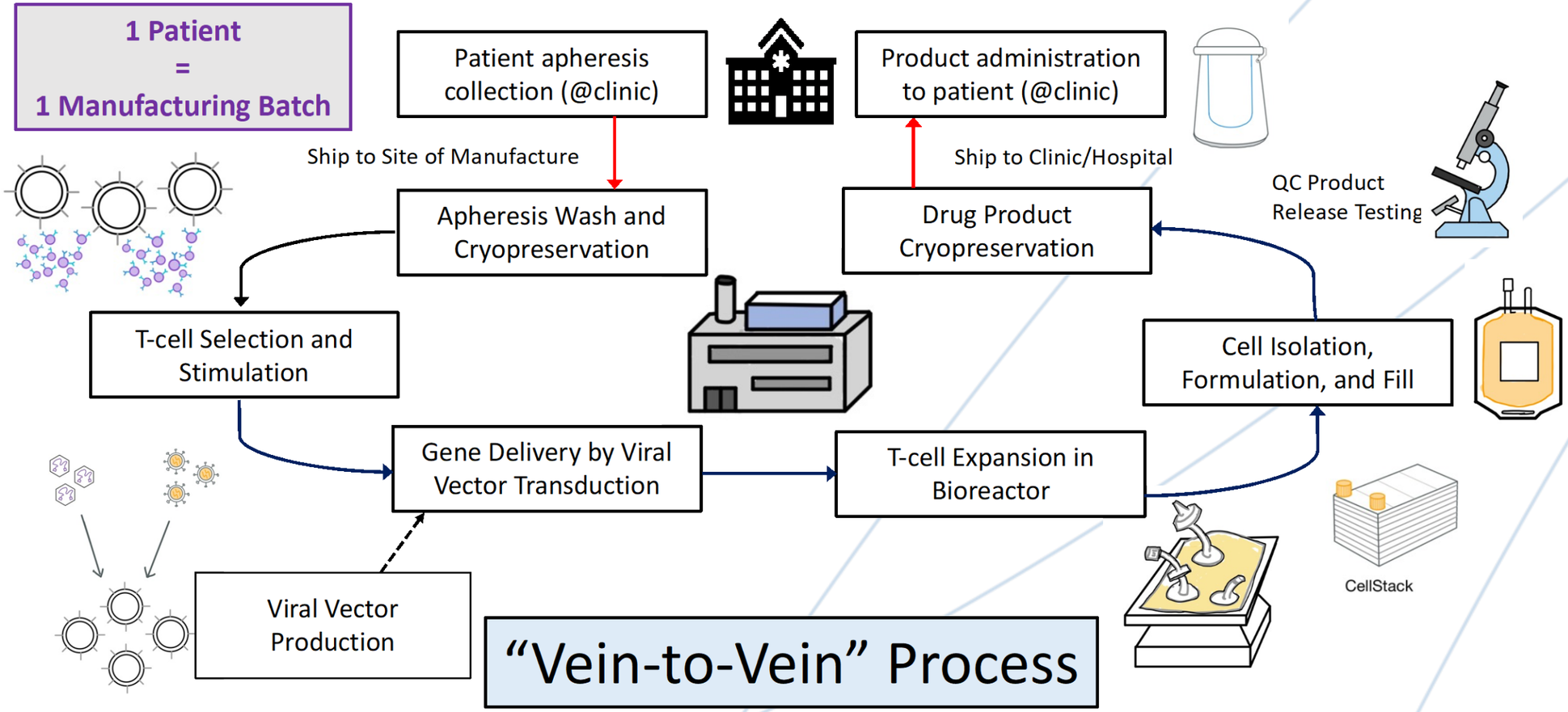
Risk-Based Approach to Change

Unique Considerations for Comparability Design for ATMPs

Product Category	Unique Considerations
Autologous (patient-specific) cellular-based therapies	Due to the variability associated with the quality of the cellular starting material, a split-batch design can be utilized (more details on the next slide)
Allogenic HLA-donor matched	Comparability between multiple donors (and even for a single donor) as the source of the cellular starting material must be considered
Viral vectors (e.g., Lentivirus) used for gene transfer for a cellular-based therapy	Significant changes to the manufacturing process for critical components / materials should perform comparability, as well as comparability of the Drug Product process
Tissue-Engineered Medicinal Products (TEMPs)	The combination of cells and scaffolds to generate the DP, thus any changes to their individual manufacturing processes require comparability also of the final Drug Product

Risk-Based Approach to Change

The Autologous Gene-Modified Cell Therapy Manufacturing Process



Design of the Comparability Study

Special Considerations for an Autologous Cell Therapy

Surrogate cellular starting material: use of donor-derived in place of patient-derived

(1) the limited availability of patient-derived CSM, as well as limitations due to informed consent restrictions

(2) The process controls and testing can be considered representative of the manufacturing performance.

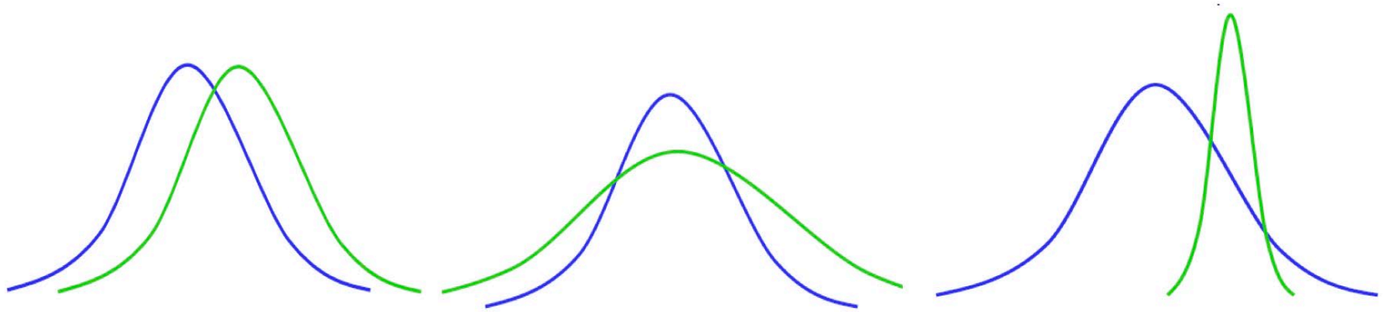


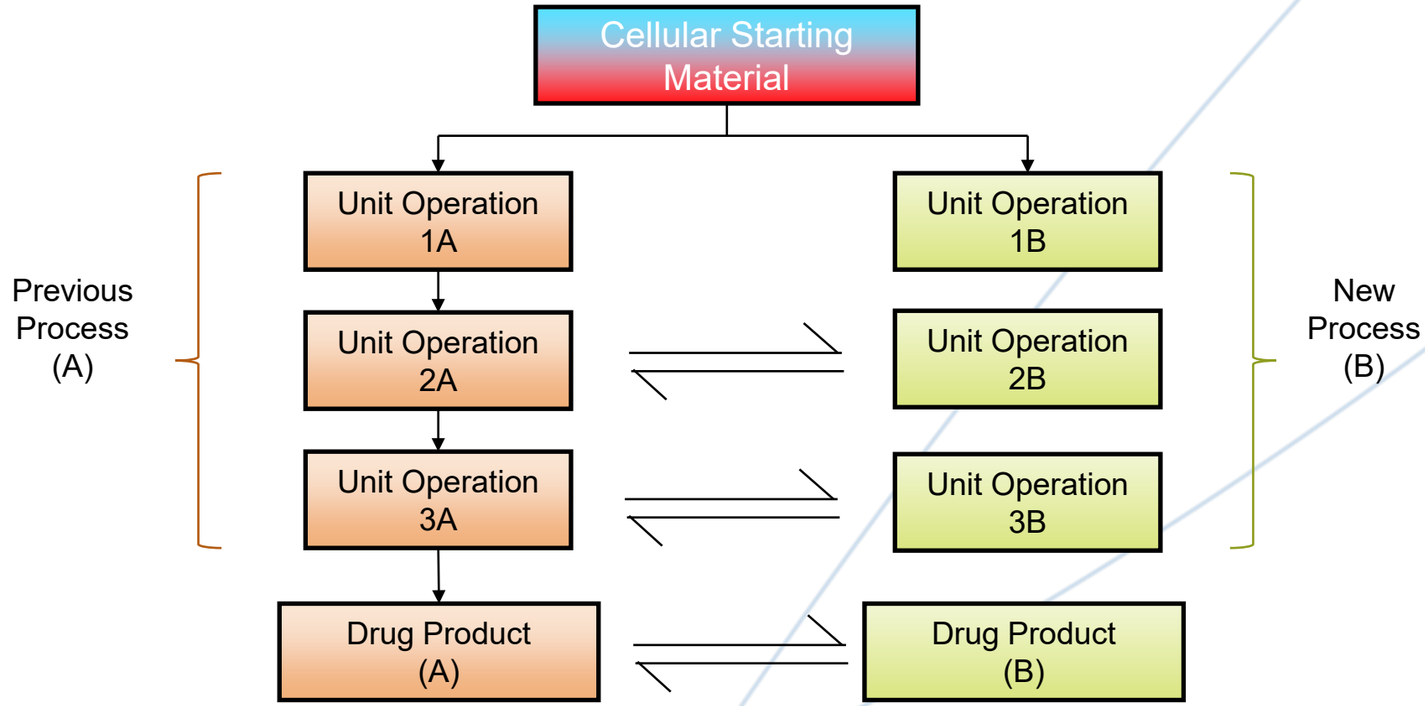
Figure 1 *Figure 2* *Figure 3*

Evaluate relationship of the DP quality attributes manufactured with cellular starting material: Patient-derived vs. Donor-derived

Design of the Comparability Study

Understand sources of variability: $\sigma_{overall} = \sqrt{\sigma^2_{process} + \sigma^2_{analytical} + \sigma^2_{CSM}}$

Specific considerations for ATMPs like autologous cell-based therapies (e.g., CAR T, TCR, NK) using cellular starting material can use a split-source study design…



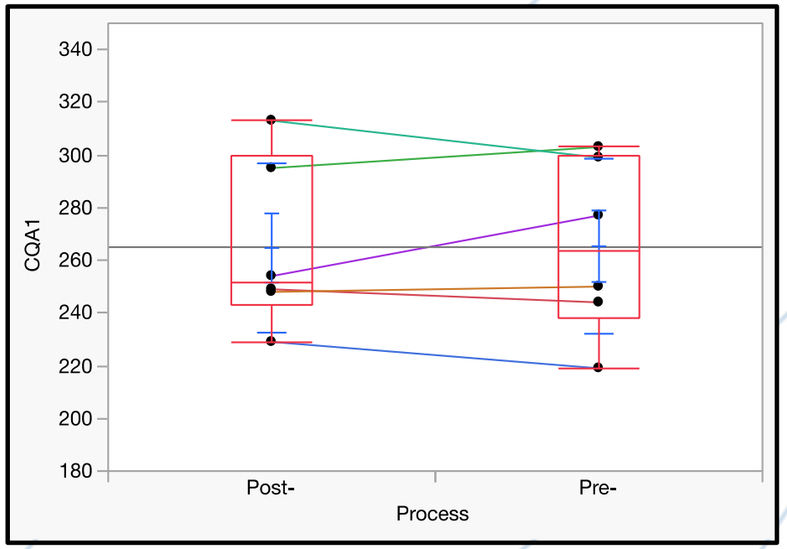
FOR MORE ON THIS: Planning Split-Apheresis Designs for Demonstrating Comparability of Cellular and Gene Therapy Products: https://pubmed.ncbi.nlm.nih.gov/39285085/

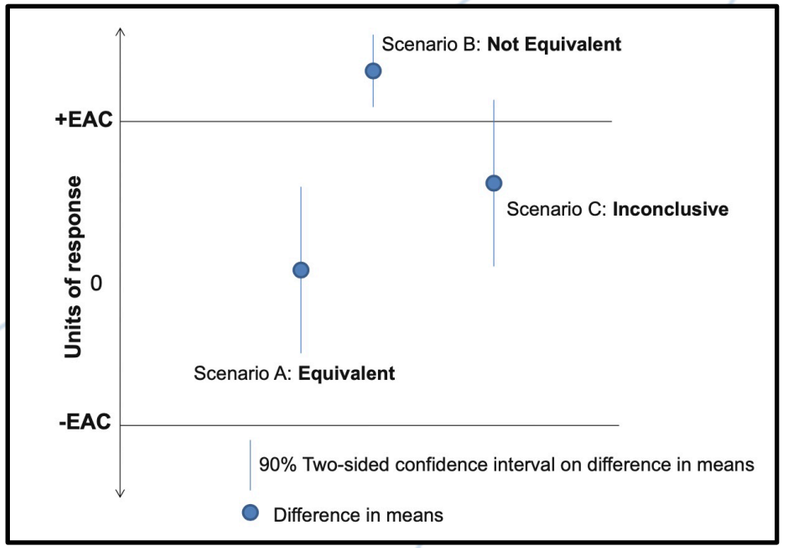
Design of the Comparability Study

Considerations for an Autologous Cell Therapy

- **Equivalence Approach**: applied to the high risk attributes
- **Quality Approach**: applied to the moderate to low risk attributes

"It is not necessary for the measurements of pre- and post-change CQAs to be identical to reach a conclusion of comparability if there is evidence demonstrating that there is no adverse impact of the change on product quality." (FDA Draft Guidance)





FOR MORE ON THIS: Consult with an experienced, qualified CMC statistician!

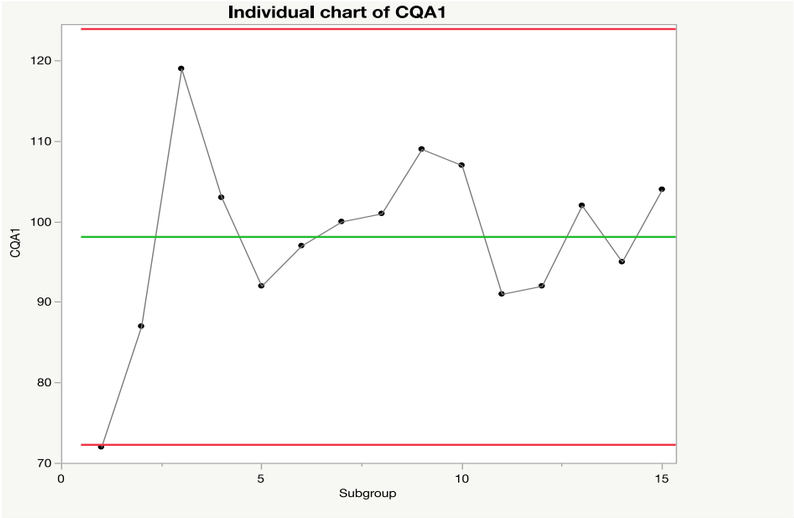
Design of the Comparability Study

Post (Successful) Comparability Process Monitoring

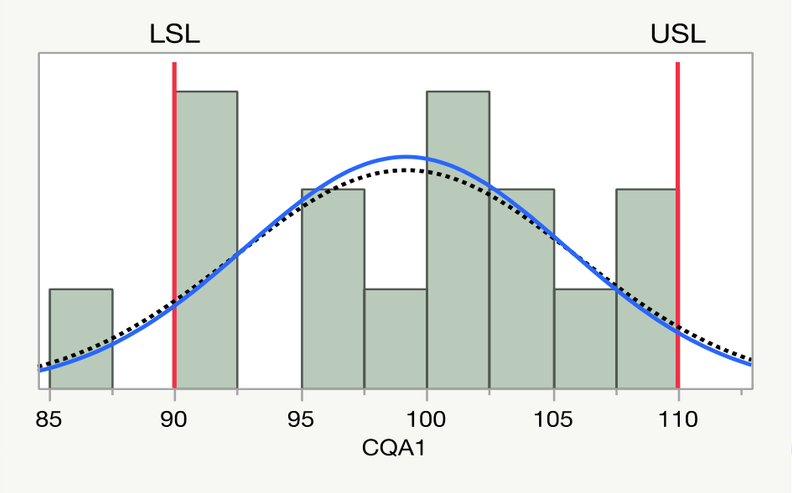
Long-term monitoring post successful implementation:

- Did the change do what it was intended (designed) to do?
- Are there any unintended consequences due to the change?
- Document and communicate the on-going process monitoring as required (e.g., updates to regulatory filing, control strategy)

Process Control Charts



Process Capability

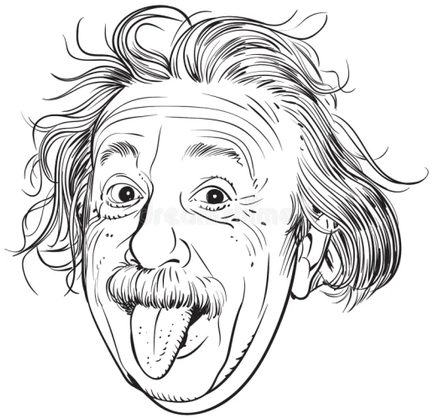


…and in Conclusion

Do not fear Change…Embrace it!

Employ a science-driven and risk-based approach to change and your organization can speed the development and commercialization of ATMPs for patients in need!

Thank you all for your time today and I am looking forward to our Q&A Session.



“The measure of intelligence is the ability to change” – Albert Einstein

And you can always reach out to keep this exciting conversation going! Thanks!