Manufacturing Challenges for Commercialization of Innovative Cell, and Gene therapy Products

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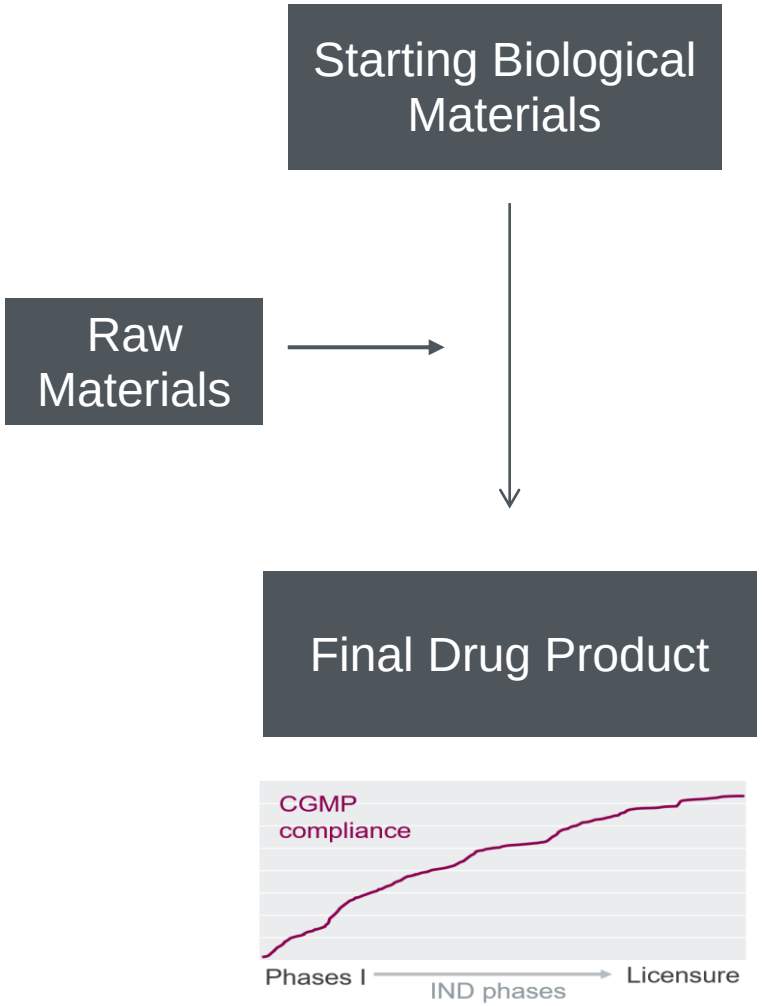
Agenda

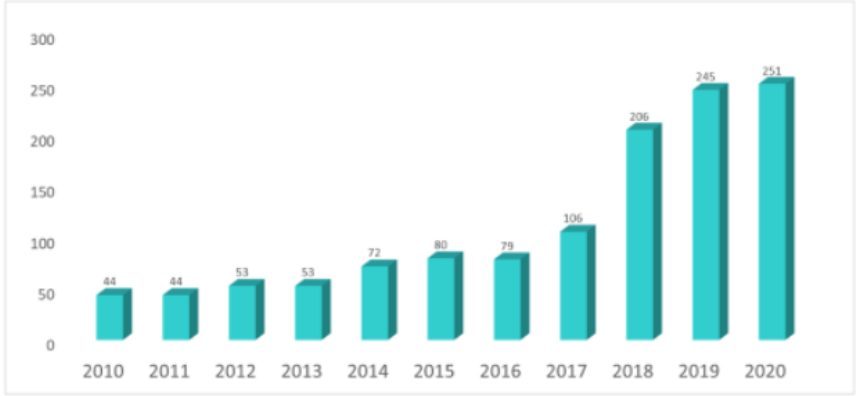
- Introduction
- Challenges in manufacturing of cell and gene therapy products
  - Product not specified and defined by process
  - Current Good Manufacturing Practices
  - Product knowledge (CQA/CPP/KPP)
  - Need for reference materials/standards
  - Matrix based approach to potency assay
  - Quality of materials, reliability of supply chain and cost of materials
  - Standardization of starting material collection
  - Rapid tests for release requiring small samples
  - Dealing with manufacturing changes
  - Contract manufacturing and labor force shortage
- Possible Solutions
- Recommendations



Summary of presentation by OTAT Office Director

- Wilson Bryan (Office Director OTAT)*
- Try to hit a home run
- Products to treat rare diseases can get FDA approval based on studies in a small number of patient
- Single arm studies are feasible
- Design FIH trial to provide evidence of effectiveness
- Resolve Manufacturing issues as much as possible
- When preclinical studies are beginning, draft the design of clinical studies
- Design and conduct natural history studies that will support subsequent drug development

Investigational New Drug Applications (INDs) for Gene Therapy Products, 2010 – 2020



FDA-Approved Gene Therapies

	Rare Disease	Single-arm Study	Efficacy Outcome not in nature	No Alternative Drug	Endpoint assessment resistant to bias	Large Effect Size
KYMRIAH (tisagenlecleucel)	✓	✓	✓	✓	✓	✓
YESCARTA (axicabtagene ciloleucel)	✓	✓	✓	✓	✓	✓
TECARTUS (brexucabtagene autoleucel)	✓	✓	✓	✓	✓	✓
BREYANZI (lisocabtagene maraleucel)	✓	✓	✓	✗	✓	✓
ZOLGENSMA (onasemnogene abeparvovec-xioi)	✓	✓	✓	✗	✓	✓
LUXTURNA (voretigene neparvovec-rzyl)	✓	✗	—	✓	✗	✓

www.fda.gov

*IFPAC-2021 Gene Therapy: Efficient Drug Development Wilson W. Bryan

It is a complicated journey and manufacturing is behind

Establishing manufacturing control is challenging

RF TODAY

Establishing Manufacturing Controls: A Hurdle for the Cell and Gene Therapy Industry

25 April 2019

Addressing manufacturing controls for the cell and gene therapy industry, this article discusses criticality of establishing Chemistry Manufacturing Controls (CMC) Readiness, Critical Quality Attributes (CQAs) and Critical Process Parameters (CPPs) for cell and gene therapy products. READ MORE >

Establishing Manufacturing Controls: A Hurdle for the Cell and Gene Therapy Industry | RAPS

Appendix A. Suggested Points to Consider and Guidance Documents
• how to establish comparability for biological products which are complex
• how to qualify and validate critical assays for biological products
• establishing potency assays
• establishing CQA, CPP and KPP for biological products which are complex (QbD approach)
• release of fresh product or products with limited shelf life
• applying principles of continuous manufacturing to complex biologics
• regulating off-the shelf product which are manufactured from small bank and selected for patients based on an "algorithm"
• developing rapid assays for sterility and endotoxin
• validation requirements for software used for making decision during manufacturing
• essential elements of manufacturing facility for gene therapy products
• aseptic process validation in manufacturing of complex biologics
• identifying and characterizing particulates in the cellular product
• expectation for extractable and leachable studies for materials with direct product contact in manufacturing of complex biologics
• process validation for autologous cellular product
• special considerations for release of product having a very small volume (autologous) or lot size (off-the shelf)
• manufacturing of induced pluripotency stem cells
• FDA expectation for CMC readiness for initiation and accelerated development of complex biologics having received expedited program designation such as breakthrough or RMAT
• alternative approaches to establishing non clinical safety and proof of concept data not requiring animal studies
• using Next Generation Sequence (NGS) for manufacturing and release of the product
• collection of starting biological materials
• manufacturing/processing and testing of the final drug product at the clinical site
• regulatory considerations for point of care or bedside manufacturing

CMC readiness checklist, possible solutions to CMC & manufacturing challenges

- Have you performed a careful review of your manufacturing process to ensure that you are entering Phase III trials with a product which is optimal?
- Have you introduced major manufacturing changes that may require conducting comparability studies and if so what is your plan to conduct such comparability studies?
- What is the status of your analytical method development. Have you qualified or preferably validated your assays prior to initiation of your pivotal trial?
- Do you have appropriate potency assays in place for the final drug product?
- Do you have knowledge of Critical Quality Attributes (CQA), Critical Process Parameter (CPP), and Key Process Parameters (KPP)?
- Have you determined shelf life of the final drug product by conducting stability assays using assays which are appropriate and qualified/validated?
- Do you have a well-defined plan to collect materials, reserve samples, for in-process and the final drug product?
- What is your plan of action to conduct process validation to demonstrate that the final drug product can be successfully manufactured consistently?
- Have you defined Standard Operating Procedures (SOP) and protocols, instructions for use outlining any additional manufacturing, processing, formulation or thaw/dilution of the final drug product at clinical sites?
- Do you plan to gain a better understanding of the requirements for conducting leachable and extractable studies for materials which are in direct conduct with your product?
- What is your plan for manufacturing of the final drug product? Do you anticipate needing to make a change to your existing facility? Do you plan for automation, scale-out or scale-up post approval or prior to initiation of Phase III study?
- Have you made a final determination if the current release specifications are adequate for ensuring safety and potency of your final drug product?
- Have you conducted shipping validation for source materials and the final drug product under worst case scenarios or conditions of transport?
- Have you reviewed the quality of ancillary materials, reliability and sustainability of your supply chain and do you have a plan to review your quality agreements and SOPPs which are in place for material qualification, vendor qualification? Have you developed an identity test for your critical ancillary materials?
- Have you finalized your choice of the final container and have a plan how to affix the label on the final drug product?
- What is your plan for testing of the source material, in process materials or the final drug product? Do you plan to outsource your testing, or will it be conducted in house?
- Do you need to develop any in house standards (physical or performance standards) for your assays? Do you know what standards are needed for your product development and release testing?
- Have you had an EOP2 or other meeting with the agency to assess your CMC readiness?

Key Questions to Consider When Licensing Cell & Gene Therapy Products | Parexel International

General challenges in cell and gene therapy product manufacturing

- Starting material
  - Donor to donor variability
  - Critical materials
- Product is defined by a process
  - Small changes in the process can have large effects on the product
- Product quality assessment
  - Critical quality attributes and critical process parameters are challenging to establish
- Commercial scale manufacturing is challenging
- Dealing with Manufacturing changes is difficult

Challenges with regenerative medicine products

- Product considerations
  - Challenges in collection of source material
  - Compliance with donor eligibility requirements (allogeneic products)
  - Donor to donor variability of biological starting material
  - Lack of suitable potency assays
  - Lack of well defined and consistently manufactured clinical grade materials
  - Limited sample volume for QC
  - Limited shelf life for fresh products
  - Challenges in product manufacturing, storage, preparation (thaw and wash) and administration at clinical sites
  - Route of administration and delivery device(s)
- Manufacturing considerations
  - Complex sometime very manual and laborious manufacturing process
  - Multiple sources of inherent product variability
  - Commercial scale product manufacturing (consistent, cost effective)
  - Scale out or scale up considerations
  - Establishing product comparability

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Consistent and high quality product manufacturing

Current Good Manufacturing Practices

- Quality standards are evolving
- Key principles of CGMPs
  - Prevent contamination and cross contamination
  - Establish consistent manufacturing of high quality product

Consistent and high quality product manufacturing

Current Good Manufacturing Practices

- Phase based approach
- Phase I (Statutory CGMPs)
- Full CGMPs verified at time of pre-license Inspection:
- PHS Act, Section 351(a) and FD&C Act
  - Federal applicable regulations:
  - 21 CFR 210, 211 (CGMPs)
  - 21 CFR 600 (biological products)
  - 21 CFR 1271, human cell, tissues and cellular and tissue based products
  - 21 CFR 800 (device)

Consistent and high quality product manufacturing

Knowledge of product

- What is the product?
  - Target product profile (TPP)
- How it works?
  - Mechanism of action (MOA)
- Critical quality attributes (CQA)
- Critical process parameters (CPP)
- Risk assessment

Sequential elements of achieving manufacturing control through understanding of the product

MOA Proposed mechanism of action for the product

TPP Target product profile characteristic required for achieving certain clinical outcome

CQA Attributes useful for determining product quality, safety and efficacy

CPP Critical process parameters which are linked to CQAs

KPP Key process parameters independent of CQAs

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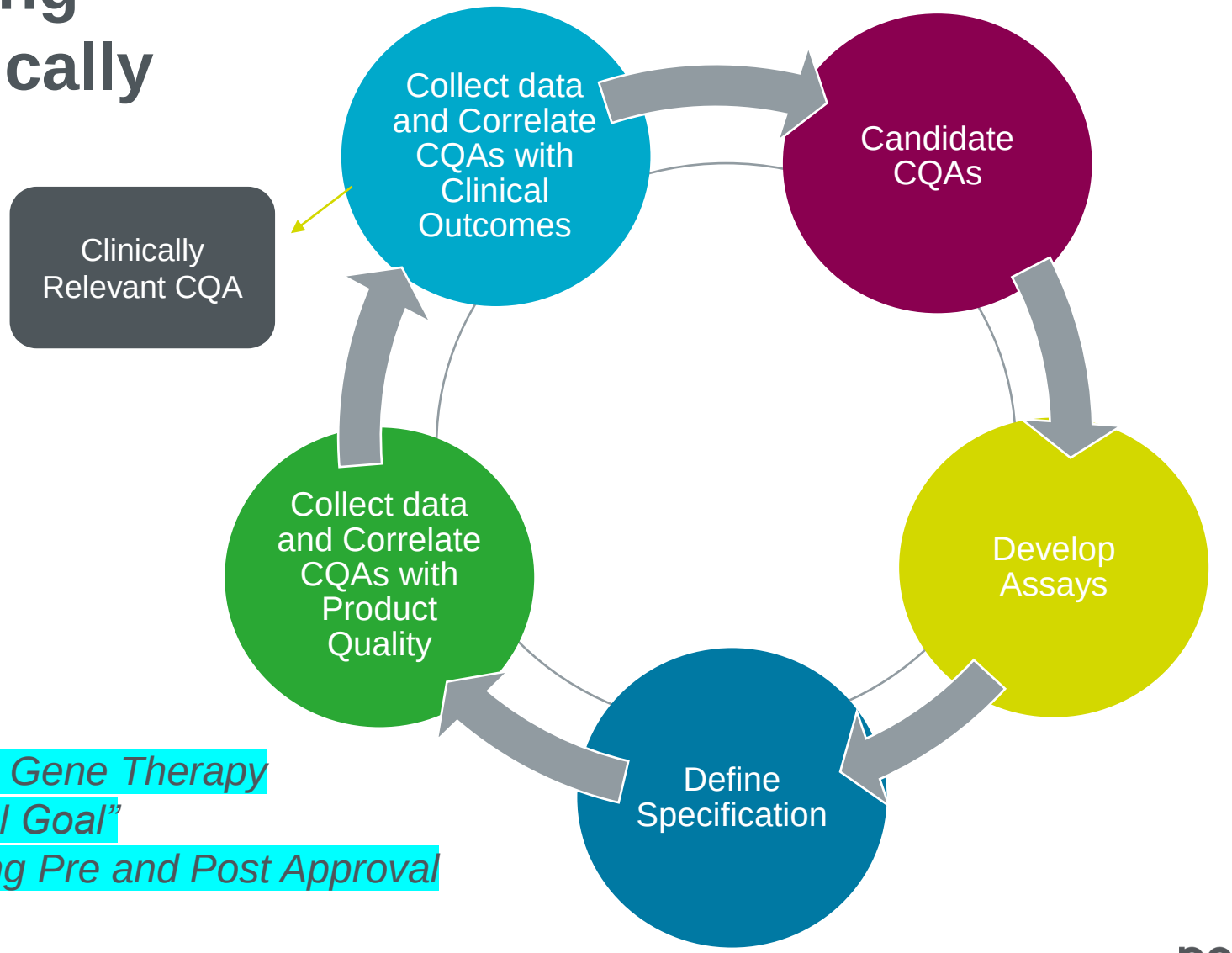
Performing a Risk Assessment

Risk assessment links the CQA and CPP with the product quality

- Risk assessment is not a good substitute for lack of product knowledge
- It is science based
- It is performed early in product development cycle and repeated when additional knowledge of product becomes available
- Risk assessment tools are found in ICH Q9

Systematic and Iterative Approach to Identifying CQAs which are Clinically Relevant



Difficult Task to Accomplish for Cell and Gene Therapy
It should be Considered as "Aspirational Goal"
Opportunity for Expediting Manufacturing Pre and Post Approval

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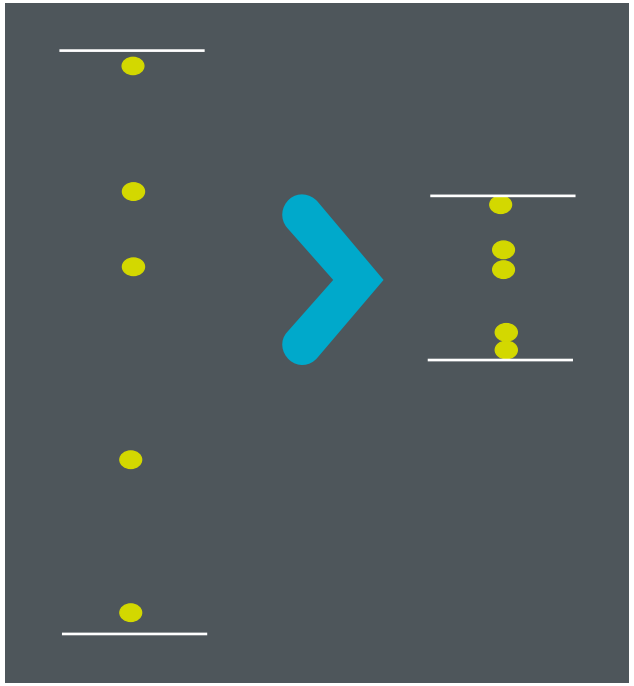
Specifications and analytical method development

Defining meaningful specifications

Specification are test method(s), procedures and acceptance criteria

- Define specification as a range with lower and upper limit
- The boundaries are defined based on historical data and inherent assay variability
- Throughout clinical trial identify sources of process and assay variabilities to better define the acceptable range

Example:



Assay or analytical method development considerations

- What is being tested (are you measuring the right attribute)
  - Attributes that reflect product quality, safety and potentially efficacy
- What is a suitable method?
  - Is method appropriate and sensitive and accurate
- Is the method under control?
  - If you ran the same sample again, would you get the same result?

Analytical assays – qualification and validation

Qualification

- Demonstration that an assay is suitable for measuring the analyte
  - Sensitive
  - Accurate
  - Reproducible (identical sample measured at two different time in same lab give similar results)
  - Requirement for Early Phase

Most Commonly Used Assays Require Qualification and Validation. If Compendial Methods are used you must follow the sampling Requirements

Validation

- Demonstration that assay is suitable for the intended use under worst condition of use
  - Sensitive
  - Accurate
  - Precision
  - Robustness
  - Ruggedness
  - Assay gives similar results when identical samples are tested in different labs, by different operators
  - Requirement for Late Phase & Licensure

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Establishing a potency assay

- Potency assay arguably the most important assay
- It is laborious and difficult to qualify/validate
- FDA recommends developing potency assay as early as possible by evaluating multiple assays
- A potency assay has to be in place by Phase III and validated for licensure
- Should be guided by MOA
- Potency assay is defined in 21 CFR 600.3(s)
- Defined as a biological assay which could be in vitro or in vivo that measure specific activity of the product

Interpretation: Every lot released should have similar potency as lot used in clinical study that determined efficacy

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How to Deal with Process Change(s)

- Process changes are inevitable
- Sponsor are responsible to plan for changes, report and implement changes.
- During IND Phase major changes are reported in amendment
- Major Changes require establishment of comparability study (case by case and depends on various factors, including timing of change, product knowledge, etc)
- Risk and science based
  - Scale up scale out
  - Automation
  - Change of critical reagents
  - Manufacturing site change

  - Examples; Company X has initiated IND with product manufactured in an academic center. They want to initiate pivotal study manufacturing the product in a GMP compliant contract manufacturing facility
  - Company X has generated data in Europe with product manufactured in Europe and wants to use the clinical data in US to initiate an IND, a pivotal study. The product will be manufactured in US

- Product comparability is intended to demonstrate that a change in process does not adversely impact product quality.
- Demonstrate product before and after change are similar not identical
- ICH Q5E states that comparability can be established using in vitro or non clinical study. In some cases if in vitro or preclinical studies are not sufficient then additional clinical study may be required.
  - ICH Q5E does not necessarily cover cell and gene therapy products
  - Questions and answers Comparability considerations for Advanced Therapy Medicinal products (ATMP)
  - Regulatory Authorities are encouraged to developed guidance documents which are suitable for establishing the comparability of cell and gene therapy products

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Tools for establishing comparability

- If CQA/CPP are well known and a correlation between CQAs and product quality, safety and efficacy can be demonstrated then testing of the product CQA before and after change is sufficient
- If knowledge of CQA/CPP is not complete then a matrix based approach is recommended
  - Compare all relevant product attributes before and after change (full/extended characterization)
    - In process and final release
    - Comparing release specifications for the product before and after change may not be sufficient
  - Manufacturing yield
  - Control of Key Process Parameters
  - Risk assessment
  - Process validation ensure consistency of product after major changes are introduced

Comparability study

- Major considerations
  - What is the change?
  - What is the level of risk impacting product quality?
  - Why the proposed change is introduced?
  - When is the product lifecycle the proposed change is introduced

The more reflective CQAs are of clinical outcome, the easier it is to establish product comparability

- Essential aspects of the comparability study
  - Risk assessment
  - A description of proposed change
  - A rationale for the proposed changes
  - Comparability study designs
  - Comparative assessment of quality attributes before and after change
  - Side by side comparison using the same biological source material is preferred
  - Justification for a well defined acceptance criteria for establishing analytical comparability
  - Detailed analytical procedure, sample plan and statistical method and analysis

https://regulatory.parexel.com/regulatory-blog/points-to-consider-for-establishing-biotechnological-biological-product-comparability

Tips to Ensure Product Comparability in Gene Therapy (genengnews.com)

Special consideration long term follow up

LTFU is not needed for all gene therapy products

Product/Vector Type	Propensity to Modify Genome[1]	Long Term Follow-up Observations[2]
Plasmid	No	No
RNA	No	No
Poxvirus	No	No
Adenovirus	No	No
Adeno-associated virus[3]	No	Product specific
Herpesvirus	No, but may undergo latency/reactivation	Yes
Gammaretrovirus	Yes	Yes
Lentivirus	Yes	Yes
Transposon elements	Yes	Product specific
Microbial vectors for gene therapy (MVGT)[4]	No, but may persist and undergo reactivation	Product specific
Genome editing products	Yes; permanent changes to the host genome	Yes

[1] Based on product design (i.e., lack of any known mechanism to facilitate integration or genome editing), as well as cumulative preclinical and clinical evidence suggesting that a GT product does not integrate into or edit the genome or integrates in/modifies the genome at very low frequencies.
[2] Specific circumstances that indicate persistent expression of the transgene, in the absence of integration or genome editing, may be the basis for a conclusion that LTFU observations are recommended to mitigate long term risks to subjects receiving these vectors. This would depend on additional criteria, such as the transgene expressed or clinical indication, as described in this section.
[3] Replication-negative vectors only.
[4] For additional guidance we refer you to "Recommendations for Microbial Vectors used for Gene Therapy; Guidance for Industry" dated September 2016, https://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/default.htm.

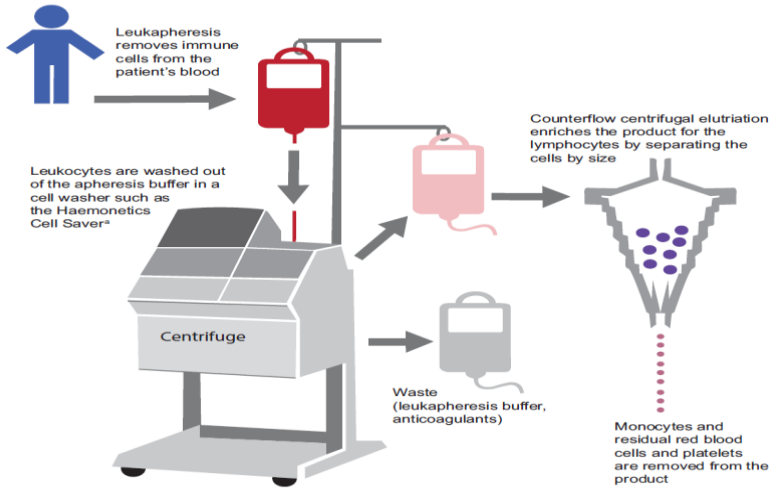
- Primary purpose to assess long term safety and durability
- The design of LTFU study depends on many factors including the exact product characteristics and indication
- Collection of additional information could be helpful

Long Term Follow-up After Administration of Human Gene Therapy Products | FDA

Other considerations

Qualification of collection materials (starting material qualification)

- Starting Biological Materials
  - Apheresis Procedure
  - Device Considerations
  - Collection, Apheresis
    - Spectra Optia, COBE Spectra (Terumo)



Bruce Levine in Molecular Therapies Methods and Clinical Development

- Cell Enrichment Step
  - Selection Platform
    - CliniMacs
    - Flow
    - Others
  - Purity of selected Population
    - Starting material characterization and qualification

The Importance of Collection, Processing and Biopreservation Best Practices in Determining CAR-T Starting Material Quality

Lou Juliano, George Eastwood, Todd Berard & Aby J Mathew, PhD

Supply chain considerations

- Supply of materials (components)
  - Raw materials, ancillary materials, equipment, containers
    - Source material collection equipment
    - Media and growth factors, others
    - Manufacturing tools (flask, bags etc.)
    - Container closures (bags or vials)
    - QC test platforms
- Grade of materials (CGMP) alone is not sufficient to ensure quality
- Shipping, and storage conditions are sometime challenging
- Cost is a factor
- FDA cleared devices, containers are preferred

- Material qualification
  - Verify safety, identity, purity and potency
  - Certificate of analysis is not necessarily sufficient
  - Quality (fit for purpose) and reliability
  - Regulation requires that manufacturers test the incoming materials for identity (Licensure)
- Vendor qualification
  - Vendors of critical materials should undergo a routine qualification process which may involve audit and/or verification of their good manufacturing practices
- Quality agreements
  - Manufacturer should have a quality agreement in place with key vendors particularly those that perform contact manufacturing. This agreement defines the relationship between the manufacturer and contract manufacturers
- Alternative sources (supply chain uncertainty)
  - Determine long term sustainability of the supply
  - Determine potential alternative Sources

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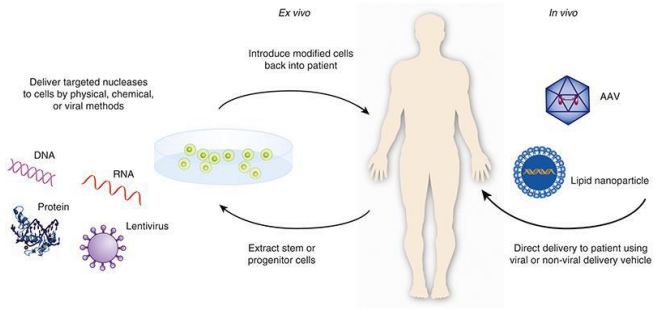
Vector quality considerations

- Background
  - Plasmids are commonly manufactured by contract manufacturers
  - Plasmid vectors are produced with different qualities
  - Recommend using CGMP grade if possible
    - CGMP grade is not verified by FDA
    - IND holder responsibility to verify CGMP compliance by contract manufacturer
- Identity Consideration
  - Full sequence analysis
  - Residual host protein and genomic DNA
  - Ensure purity (lack of cross contamination)
    - Adherence to CGMP principles
    - Cross contamination control
      - Line clearance
      - Product specific cleaning validation of contact surfaces
      - Appropriate monitoring and environmental controls and classification
  - Appropriate quality standards
    - Appropriate release tests

https://www.biopharma-reporter.com/Article/2018/07/27/US-FDA-puts-gene-therapy-on-hold-after-DNA-fragment-found-in-plasmids#.W18o9r4gEnQ.linkedin

Special consideration for gene editing (GE)

- Common Platforms: Cas9/TALEN
- Used for generating variety of Indels and deletions
- Review of risk benefit analysis is performed case by case and dependent on target indication, type of gene editing (in vivo or ex vivo), platform(s) utility, and safety and knowledge of the final drug product.
- GE components can be introduced to cells by variety of methods (Introduce expression vector or modified viruses or deliver nuclease and RNA guide LNPs)



FDA Science Board Meeting

November 15, 2016

- Characterization of On target editing and allele composition
- Discovery and verification of Off target Indel formation, and large inter or intra chromosomal changes (deletion, translocation, etc.) through biased and unbiased genome wide off-target identification (orthogonal approach)
- Demonstrate that ex vivo edited cellular product does not contain any nuclease activity
- Demonstrate quality of gene editing components:
  - Quality, stability, purity, identity, sterility
  - Description of optimization steps for components used
- Detailed description of gene or protein delivery platforms (electroporation, others)
- Demonstrate adequate manufacturing experience prior to clinical product manufacturing
- Characterization of GE related toxicities impacting cell phenotype

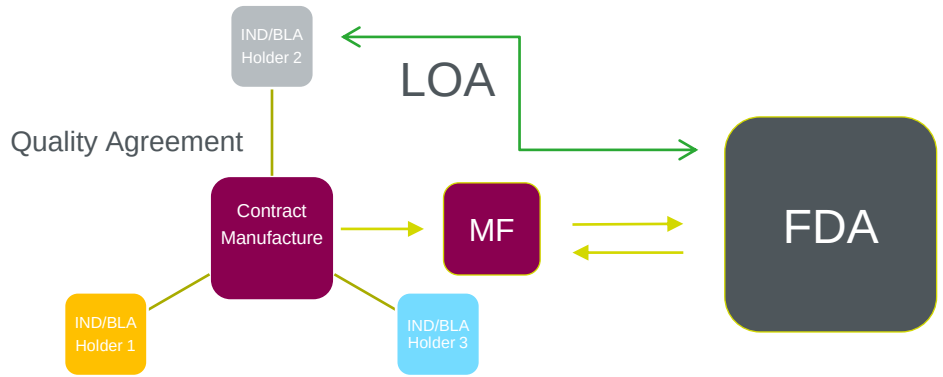
Case Study Delivery of Gene Edit Materials and Definitions

- **In vivo Gene Edit**
- Intravenous Injection
- Product: LNP/gRNA/Cas9
- Drug Substance: gRNA/Cas9
- Drug Product: LNP/gRNA/Cas9
- In vivo on target versus off target
- In vivo biodistribution
- All in vitro characterization required for ex vivo gene editing in relevant cell lines

- **Ex vivo Gene Edit**
- Patient Cells Gene Edited Ex Vivo
- Product: Gene Modified Cells
- Example of editing material LNP gRNA/Cas
- Critical Starting Material: gRNA/Cas9 protein
  - Quality is assessed similar to DS
  - Manufacturers are required to have release specification
- Stability and functionality of gene edited cells
- Gene edit efficiency
- Gene edited cells persistence and engraftment when given to patients
- In vitro characterization of off target

Special consideration contract manufacturing

- Sponsors:
  - Applicant is ultimately responsible for quality of the product
  - For BLA cross referencing the content of MF for DS/DP/DSI can not be relied upon*
  - For IND cross reference of content of MF is allowed for certain information
    - If MF is not adequate IND holder is notified of deficiencies.

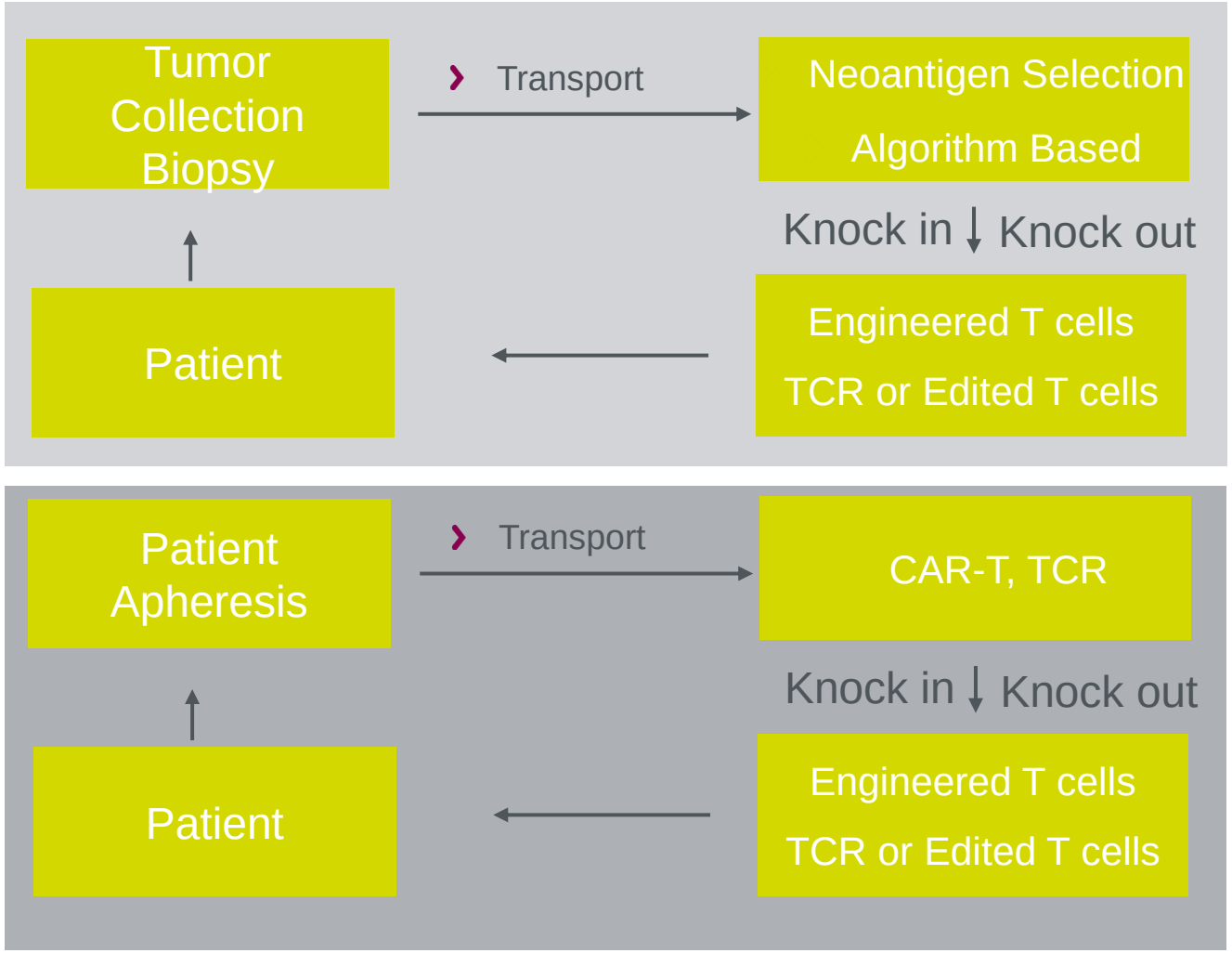


- Contract Manufacturers:
  - Sponsor relationship with contract manufacturer should be established (Quality Agreement)
  - Confidential information can be submitted to FDA in appropriate Master File
    - Type II (DS/DP/DSI) , III (packaging, CC), IV (excipients) and V (Reference/Facility) (eCTD submission requirements)
  - MF holder should provide LOA allowing FDA to review information in MF in relationship with a submission
  - CM may be inspected by FDA as part of pre license inspection

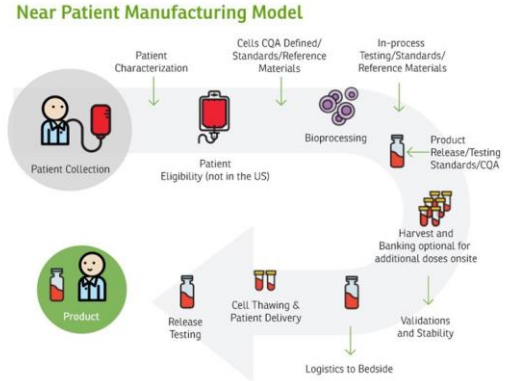
***Biologics License Applications and Master Files (https://www.federalregister.gov/documents/2019/06/28/2019-13753/biologics-license-applications-and-master-files)**

Manufacturing platform and facility considerations

Manufacturing from vein to vein (patient specific products)



- Trend toward shortening manufacturing time vein to vein
- Manufacturing facility and CGMP Compliance
  - Decentralized point of care/near patient or bedside manufacturing
  - Consideration of the manufacturing environment
  - Product quality considerations
- Trend toward single use disposables
- Automated functionally closed platforms



Manufacturing Cell Therapies: The Paradigm Shift in Health Care of This Century - National Academy of Medicine (nam.edu)

Standard Development and Manufacturing Initiatives

Standard development activities

- Standard Development in Regenerative Medicine
- 21st Century Cure Act Title III, Section 3033-3036
  - Section 3036: Direct Department of Health Services (HHS), in consultation with National Institute of Standard and Technologies (NIST) and stakeholders, to facilitate efforts around development of standards for regenerative medicine therapies and regenerative advanced therapies
    - Develop physical and Performance Standards to facilitate development of Regenerative product manufacturing and testing
    - Guidance on “Standards Development and the Use of Standards in Regulatory Submissions Reviewed in the Center for Biologics Evaluation and Research”
    - https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/General/UCM589416.pdf
  - Standard Coordinating Body (SCB)
    - SCB is a not for profit organization began as an initiative of the Alliance for Regenerative Medicine (ARM). In September 2016, the National Institute of Standards and Technology (NIST) and SCB established a Memorandum of Understanding (MOU).
    - https://www.standardscoordinatingbody.org/
    - Standard Development Bodies (Consensus and Non Consensus)
      - ISCT, ASTM, ISO, USP
    - National Institute of Standards and Technologies (NIST)

Manufacturing initiatives

- **CBER Advanced Technologies Team (CATT)**
  - https://www.fda.gov/vaccines-blood-biologics/industry-biologics/cber-advanced-technologies-team-catt
- National Institute for Innovation in Manufacturing Biopharmaceuticals (NIIMBL) https://niimbl.force.com/s/
  - Focus of developing technology to facilitate manufacturing of biologics (NIST)
  - Work force training and grant for projects to develop scale up manufacturing and rapid testing for release
  - Gene Therapy Roadmap, Vaccine Roadmap and Bispecific roadmaps
- Advanced Regenerative Medicine Institute https://www.armiusa.org/
  - Focus on Tissue Engineering and 3D printing (DOD)
- Georgia Tech Manufacturing Institute http://www.manufacturing.gatech.edu/
- National Institute of Health https://www.nih.gov/research-training/medical-research-initiatives/rmi
- FDA/CBER Enhancing Innovations in Emerging Technologies for Advanced Manufacturing of Complex Biologic Products (R01) https://grants.nih.gov/grants/guide/rfa-files/rfa-fd-18-023.html
- Continuous Manufacturing https://www.fda.gov/Drugs/NewsEvents/ucm557448.htm

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Summary

- Making quality products faster and cheaper is becoming ultimate goal of commercialization
- Adherence to GMP principles is still very important- Regulations are not changed but interpreted in view of different products
- Product knowledge is a must
- For autologous product there is trend or shift to near patient manufacturing
- Development of functionally closed system should be part of strategy- Plus automation
- Physical reference materials are lacking
- USP compendial methods should go beyond current scope
- Quality raw material which are cost effective- Develop platforms to manufacture quality gRNA, LNPs, plasmids etc.
- Rapid tests for release from weeks to days to hours
- Plan for implementing manufacturing changes (comparability study) should be in place early on
- Transition from academic to commercial manufacturing remains to be stumbling block
- Investment in contract manufacturing (Private Public Partnership)

- Encourage incremental improvement in manufacturing
  - Upstream and down stream purification for viral products
  - Viral clearance
  - Cell line development for virus productions
- NGS and novel assays for product release still require validation
- Potency assays are not necessarily biologically relevant
- CQA/CPP/KPP are not well understood
- Acceptance criteria are defined based on manufacturing capability not product quality attributes
- Collection of patient material or from healthy donors requires further standardization
- If product knowledge is sparse, process development and optimization is challenging no matter how advance the manufacturing platforms are
- Product Approval does not equate to commercial success
- Safety and effectiveness + cost effectiveness = Commercial Success

References

- Manufacturing Considerations for Licensed and Investigational Cellular and Gene Therapy Products During COVID-19 Public Health Emergency; Guidance for Industry
  1/2021
- Human Gene Therapy for Neurodegenerative Diseases; Draft Guidance for Industry
  1/2021
- Interpreting Sameness of Gene Therapy Products Under the Orphan Drug Regulations; Draft Guidance for Industry
  1/2020
- Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs); Guidance for Industry
  1/2020
- Long Term Follow-up After Administration of Human Gene Therapy Products; Guidance for Industry
  1/2020
- Testing of Retroviral Vector-Based Human Gene Therapy Products for Replication Competent Retrovirus During Product Manufacture and Patient Follow-up; Guidance for Industry
  1/2020
- Human Gene Therapy for Hemophilia; Guidance for Industry
  1/2020
- Human Gene Therapy for Rare Diseases; Guidance for Industry
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References

- Human Gene Therapy for Retinal Disorders; Guidance for Industry
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- Evaluation of Devices Used with Regenerative Medicine Advanced Therapies; Guidance for Industry
  2/2019
- Expedited Programs for Regenerative Medicine Therapies for Serious Conditions; Guidance for Industry
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- FDA Provides Guidance on Remote Interactive Evaluations for Oversight of Drug Facilities During COVID-19 | FDA
- COVID-19 Container Closure System and Component Changes: Glass Vials and Stoppers Guidance for Industry
  - https://www.fda.gov/regulatory-information/search-fda-guidance-documents/covid-19-container-closure-system-and-component-changes-glass-vials-and-stoppers-guidance-industry
- Manufacturing Considerations for Licensed and Investigational Cellular and Gene Therapy Products During COVID-19 Public Health Emergency
  - https://www.fda.gov/media/145301/download
- Resuming Normal Drug and Biologics Manufacturing Operations During the COVID-19 Public Health Emergency
  - https://www.fda.gov/media/142051/download

CBER 2021 Guidance Document Plan

- Manufacture of Blood Component Using a Pathogen Reduction Device in Blood Establishment: Question and Answers
- Revised Recommendation for Reducing the Risk of Zika Virus Transmission by Blood and Blood Components
- Interpreting Sameness of Gene Therapy Products under the Orphan Drug Designation
- Consideration of the Development of Human Gene Therapy Products Incorporating Genome Editing
- Considerations for the Development of Chimeric Antigen Receptor (CAR) T Cell Therapies
- Studying multiple versions of a cellular or gene therapy Product in a Clinical Trial
- Chemistry, Manufacturing, and Control Changes to an Approved Applications: Certain Biological Products

References

- Expedited Programs for Regenerative Medicine Therapies for Serious Conditions
- Considerations for the Design of Early Phase Trial for Cellular and Gene Therapy Products
- Formal Meeting between the FDA and Sponsors or Applicants of PDUFA Products
- INTERACT Meeting (Initial Targeted Engagement for Regulatory Advice on CBER Products)
- CMC Information for Human Gene Therapy INDs
- Long term follow up After Administration of Human Gene Therapy Products
- Testing of Retroviral Vector-Based Gene Therapy Products for Replication Competent Retroviruses During Products Manufacturing and Patient Follow Up
- Human Gene Therapy for Rare Diseases

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References

- ICH Q2(R1) – Includes Validation of Analytical Procedures
- ICH Q5E – Includes concepts of comparability and how to establish comparability
- ICH Q6 – Includes concepts of quality standards, acceptance criteria and specifications
- ICH Q8 – Pharmaceutical Development:
- Includes concepts of critical quality attributes and critical process parameters
- Includes concepts of Quality by Design and examples of design space
- ICH Q9 – Quality Risk Management
- Describes a systematic process for the assessment, control, communication and review of quality risks
- ICH Q10 – Pharmaceutical Quality Systems
- Describes systems that facilitate establishment and maintenance of a state of control for process performance and product quality

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Thank you

Questions

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Gene therapy considerations

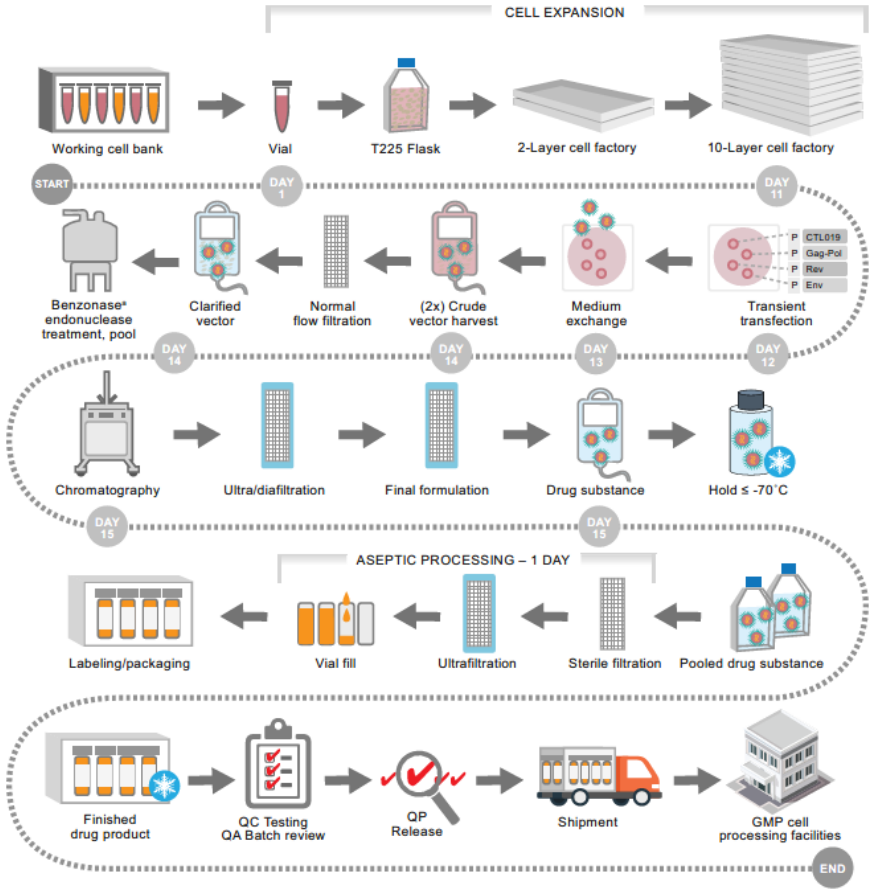
Appendix

Special consideration for gene therapy

- Manufacturing process and platforms
- Vector and plasmid sequence information
  - Cross contamination and quality of material
- Virus Information
- Special safety consideration
  - Purity of product
  - Replication Status
  - Adventitious Agent
  - Oncogenic activation and persistence or other virus specific safety consideration
- Virus shedding and patient follow up

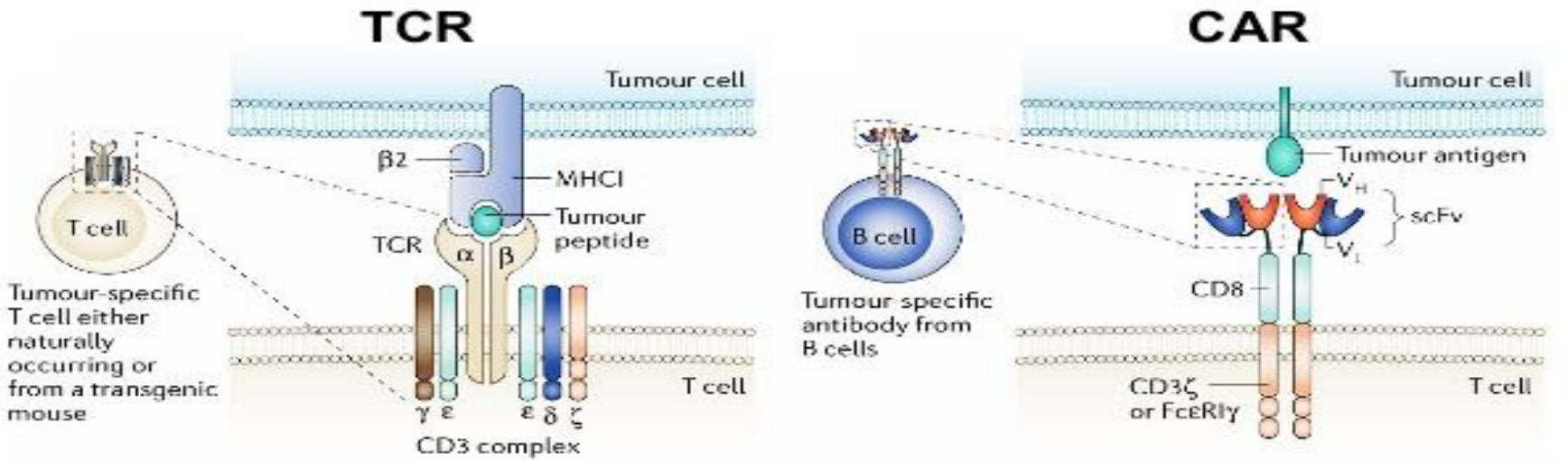
Technical and manufacturing challenges (gene modified cells)

- Purity and Composition of Transduced cells
- Efficiency of Transduction
- Risk of Replication Competent Virus
- Possibility of Insertional Activations
- Ancillary Material and Supply chain
- Manufacturing Consistency at Commercial Scale
- Manufacturing Capacity
  - Scale Out, Automation
- Chain Of Identity and Chain Of Custody
- Cost



Bruce Levine in Molecular Therapies Methods and Clinical Development

Engineered T cells CAR vs TCRs



1. Sensitive signal amplification derived by evolution
2. Low avidity
3. Targets intracellular proteome
4. Requires MHC class I expression and HLA matching on tumor cell
5. Possible mispairing with endogenous TCR

1. Signal amplification derived by synthetic biology
2. Avidity controllable
3. Targets only surface structures
4. HLA independent antigen recognition, universal application
5. No mispairing with endogenous TCR

Key safety challenge associated with engineered T cells

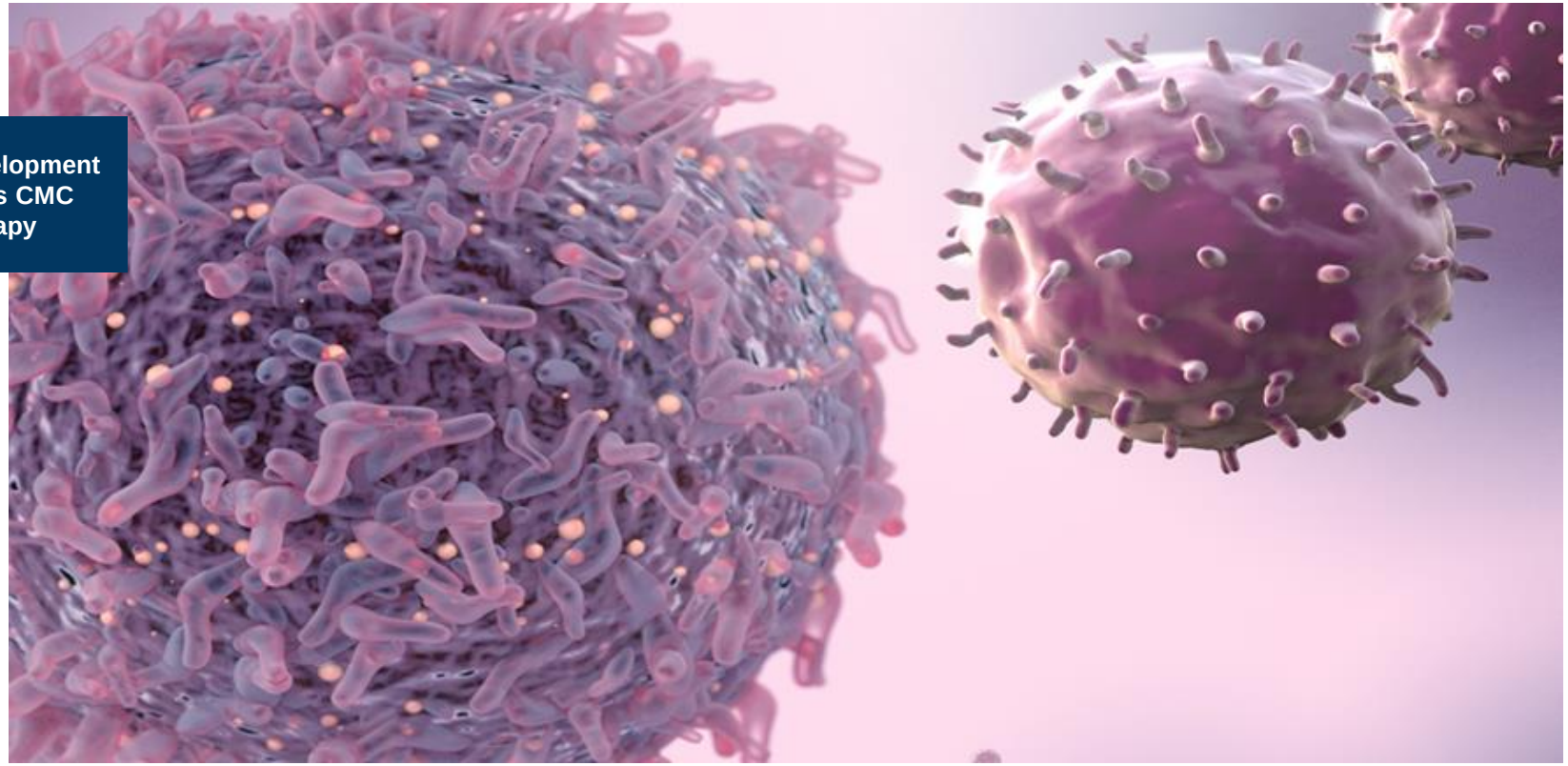
- Target selection, maximize efficacy while minimize safety concerns
- On Target Off Tumor Activity
- Cross reactivity with related proteins or related peptides in the context of targeted MHC (TCRs)
- Alloreactivity with related peptides MHC complexes (TCR)
- **Risk Mitigations:**
- Multiple methods for target expression analysis
- Multiple methods to study the interaction of the engineered T cells with normal cells
  - In vivo studies
  - In vitro studies and in Silico

Special consideration AAV technology

- Payload limit and characterization
- Quality of Ancillary Materials
- Immunogenicity (Repeat administration)
- Replication Competent Virus
- Durability of response
- Aggregate formation and filtration
- Adventitious Agent Testing (Viral Clearance)
- Empty full capsid separation and testing
- Method development and validation
- Manufacturing capacity (adherent vs. suspension cell Process)
- Cost

- **AAV Quantitation Assay is Critical (how to determine patient dose accurately)**
  - Empty to full ratio and particle to infectivity ratio
- Transgene expression, potency and stability
- Assay qualification and validation are very critical
- Methods: qPCR/ddPCR (Viral Genome Concentration; ELISA (Viral Capsid Quantification), SDS-PAGE (VP Protein Profile, Spectroscopy, Ion Exchange Chromatography (separation between empty and full capsid), Electron Microscopy (Viral particles as a population), NGS!
- FDA does not recommend use of T antigen containing cell line since there are multiple platforms available which have better safety profile
- Test for rcAAV should include qPCR for capsid sequence in addition to rep sequence following cell amplification!

Global Drug Development
Regulatory Affairs CMC
Cell & Gene Therapy



CMC Challenges for Cell and Gene Therapy Products

FDLI

Lawrence C. Starke, PhD

June 09 2021

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Cell and Gene Therapies – A new Era of Medicine

Conventional therapy	Cell and gene therapy
Molecular compound	Use of the patient's DNA cells
Chronic therapy	One-time treatment
Long-term symptom treatment	Potentially curative

Regulatory Landscape

- Rapidly evolving framework shaped by regulations, guidance documents and the interpretation of them by the regulators and product sponsors

- Current thinking of regulatory agencies captured in specific guidance documents issued at an accelerated pace around the globe. Global alignment between Health Authorities can be challenging

- Experience gained in practice

- Several regulatory mechanisms available for accelerated pathways to approval such as Regenerative Medicine Advanced Therapy (RMAT) and Breakthrough (BT) designation in US, Fast Track, Priority Review, and INTERACT meetings (Initial Targeted Engagement for Regulatory Advice on CBER products), PRIME scheme in EU, Sakigake designation in Japan

Key CMC Challenges

1. Manufacturing sites and manufacturing process

2. Quality control – raw and starting materials, analytical testing

3. Comparability in development and post - approval

CMC Challenge # 1

Manufacturing Site Considerations

- Majority of therapies developed in academic settings, need to be optimized for suitable GMP production
- Sound manufacturing facility plans needed early in drug development to assure commercial success (flexible, modular design, automation, easy to adopt new technologies, scale-up / scale-out considerations)
- Robust contamination control strategy and adherence to aseptic processing guidelines

Manufacturing Process Considerations

- Manual, labour intensive, multi-step process, small batch size due to current technologies - extensive release testing program may consume significant amount of each batch

- Variable patient material (autologous therapies), limited product knowledge and not well understood mechanism of action - impact on the development of the product to be consistently manufactured at the commercial scale

- Understanding the product CQAs/CPPs and correlating it to clinical outcomes is a critical aspect of establishing a suitable manufacturing process and controls for assuring product quality and consistency.

- Process validation approaches - use of surrogate starting material (from healthy donors) in combination with patient material

CMC Challenge # 2

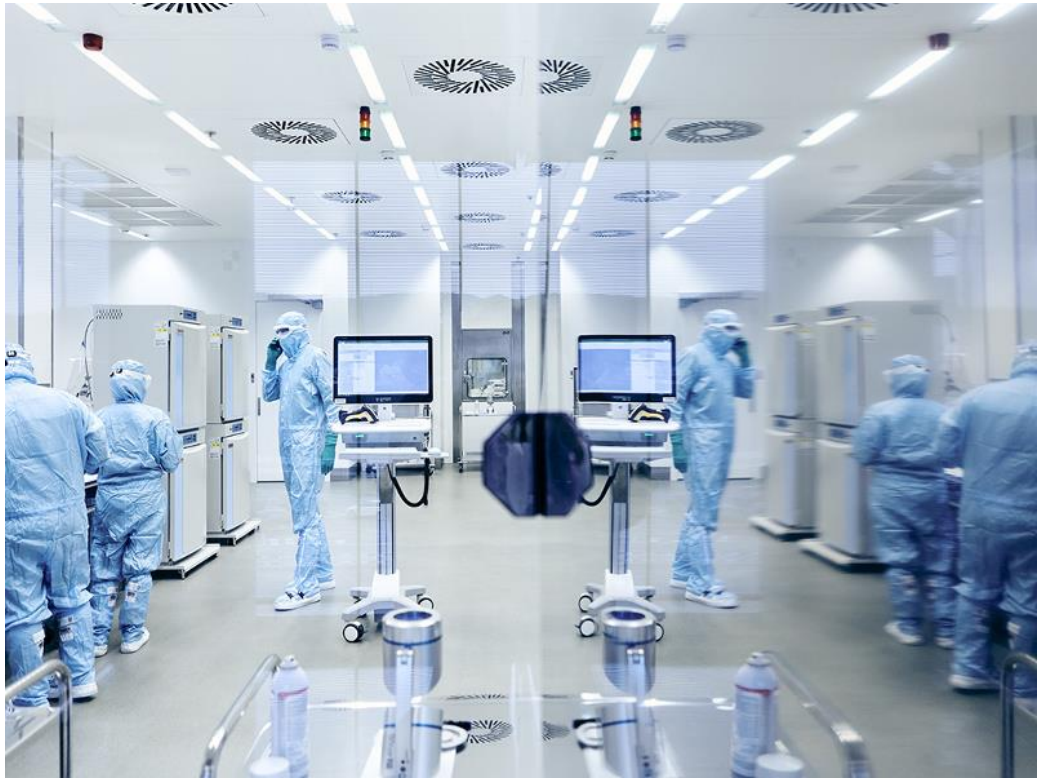
Product Quality Control Considerations

- Quality of raw and starting materials – patients variability, availability of clinical grade reagents, single source, non GMP suppliers
- Use of human and animal-derived materials – impact of lot-to-lot variability on manufacturing process and the quality of final product
- Lack of simple characterization methods for raw materials

Product Quality Control Considerations

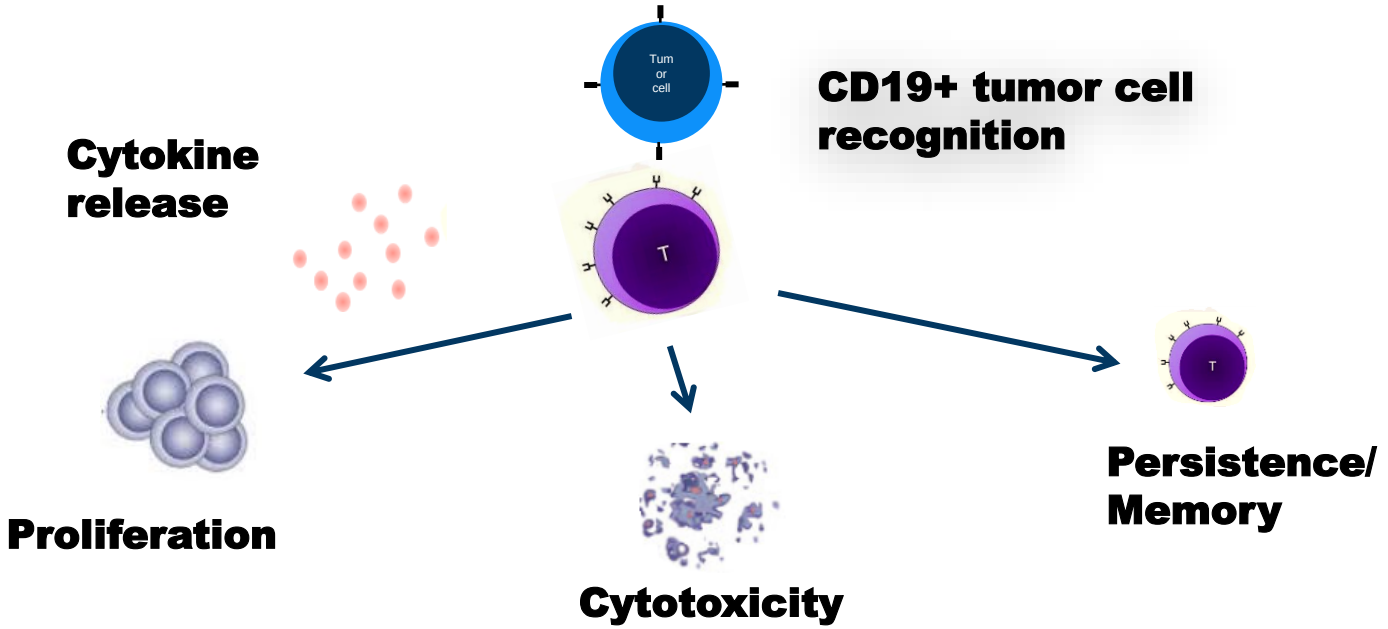
- Development of precise analytical tools to determine dose and strength, analytical methods not sufficient to fully define the product

- Setting meaningful acceptance criteria for autologous products considering limited manufacturing experience in early clinical development (e.g. 1-2 batches produced at the time of IND submission), high patient variability and variability of the analytical methods



Example: CAR-T Potency Testing

As the cell product cannot be fully characterized a comparative assessment of multiple T cell functions is key.



CMC Challenge # 3

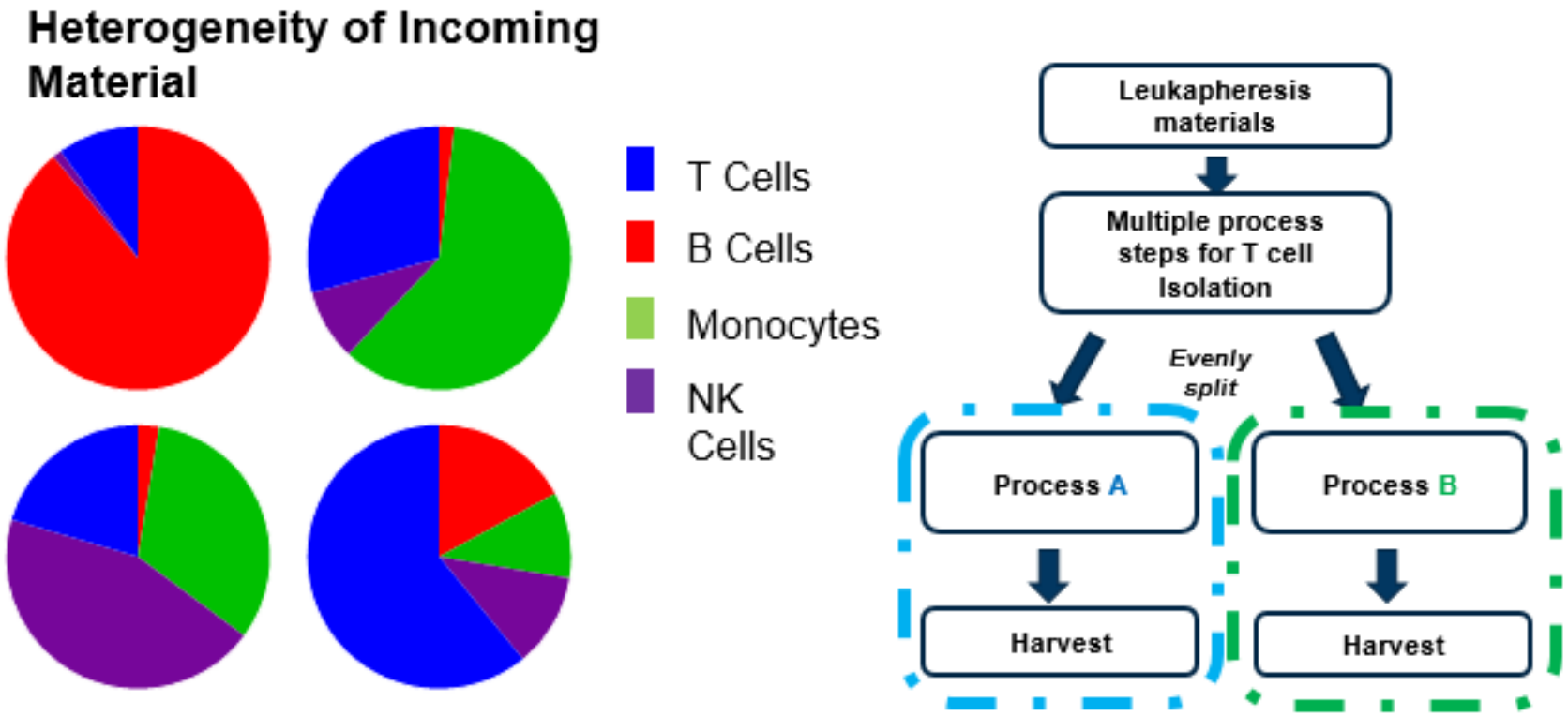
Comparability Considerations

- High rate of changes and comparability is a key exercise throughout development and post-approval
- The goal of comparability exercise is to demonstrate consistency of pre and post-change with no adverse impact on product quality, safety and efficacy
- Development of comparability plan as early as possible in clinical development is highly recommended

Comparability Related Challenges

- Inherent variability in patient material (apheresis)
- Limited manufacturing history (not enough retention/test samples available)
- Limited product characterization
- Comparability studies not statistically powered
- Analytical method availability and variability

Use of ‘Split Apheresis’ Starting Material to Minimize Unrelated Variability



Split healthy donor or patient apheresis is used to minimize unrelated variability which might be caused by different starting material in order to better assess the impact of the change.

Conclusions

- Cell and Gene therapy field is rapidly evolving due to a great promise to address unmet medical need for the treatment and potential cure of life threatening diseases
- CMC readiness is one of the most significant challenges
- Evolving regulatory framework and early dialog with Health Authorities is a key to successful development, commercialization and life cycle of the product in post approval phase

Questions?

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Thank
You
Asante
Shukria
Dhanyavadagalu
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köszönöm
Kiitos
Maake
Manana
Dankon
Matondo
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Kam Sah Hammida
Dankscheen
спасибо
Dank Je
Mauruuru
Biyan
Terima Kasih
Taiku
Tack
Blagodaram
Ngiyabonga
Dziekuje
Chokrane
Diolch i Chi
Grazie
Juspaxar
Arigato
Mochchakkeram
Gracias
Bedankt
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Paldies
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