Global Regulatory Considerations for Allogeneic Cell Therapies

Yoko Momonoi
Global Regulatory CMC Cell and Gene Therapy
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Takeda Pharmaceuticals U.S.A., Inc.

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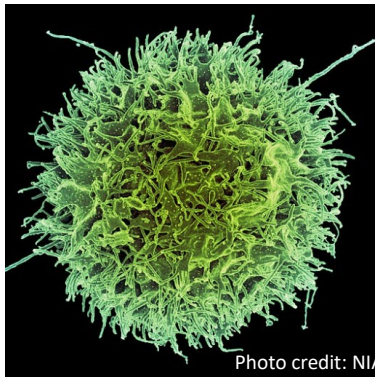
Better Health, Brighter Future

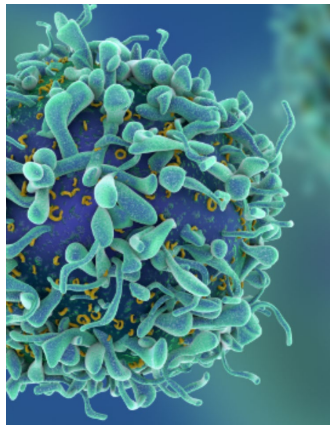
Allogeneic cell therapies at Takeda



MD Anderson Cancer Center

NK cells

Potent tumor killing cells with potential to orchestrate T cell responses



GAMMADELTA THERAPEUTICS

γδT cells

- Ability to recognize tumor cells without MHC peptide presentation reduces risk of alloreactivity
- Potent anti-tumor activity that is not antigen-specific

ALOFISEL® (darvadstrocel)

Adipose-derived mesenchymal stem cell therapy

- Approved in EU in 2018
- RMAT designation in USA in 2019
- Approved in Japan in 2021
- Approved today in 20 countries

T-CiRA

Universal cell-based iPSC platforms

- Scalable, programmable biology with vial-to-vial comparability
- Potential for multiple therapies

Spectrum of products

"Individualized"	"Off the shelf"
Autologous single product lot	Large scale allogeneic cell bank-based product

Common concerns

Mechanism of action, material qualification, challenges establishing specifications, manufacturing facility, product shipping/handling, major manufacturing changes

Specific concerns

- Product tracking and segregation
- High product variability
- Limited material or time for testing
- Short shelf life
- Manufacturing logistics
- Scale-out

- Donor eligibility
- Qualification of cell banks
- Reproducibility of replacement bank
- Stability of cell banks and intermediates
- Scale up

Source: Anna Kwilas Ph.D., *CMC Challenges during Accelerated Development of Human Cell & Gene Therapy Products A CBER Perspective*, CASSS Cell and Gene Therapy 2020

Global Regulatory Considerations for Allogeneic Cell Therapies

A risk-based and proactive approach to developing a global strategy

- Donor eligibility requirements
- GMP applicability
- Potency

Key Regulations and Guidance for Human Cell Donor Eligibility Determination

FDA 

- ***21 CFR (Code of Federal Regulations Title 21) Part 1271*** *Human cells, tissues, and cellular and tissue-based products*
- *Guidance for Industry: Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products*
- *Guidance for Industry: Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs)*

EMA 

- ***Directive 2004/23/EC*** *of the European Parliament and of the Council of 31 March 2004 on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells*
- *Commission Directive **2006/17/EC** of 8 February 2006 implementing Directive 2004/23/EC of the European Parliament and of the Council as regards certain technical requirements for the donation, procurement and testing of human tissues and cells*
- *Commission Directive **2006/86/EC** of 24 October 2006 implementing Directive 2004/23/EC of the European Parliament and of the Council as regards traceability requirements, notification of serious adverse reactions and events and certain technical requirements for the coding, processing, preservation, storage and distribution of human tissues and cells*
- *Commission Directive **2004/33/EC** of 22 March 2004 implementing Directive 2002/98/EC of the European Parliament and of the Council as regards certain technical requirements for blood and blood components*

PMDA 

- *Standards for Biological Materials (Japanese Standards of Biological Ingredients, JSBI)*
- *Implementation of the Standards for Biological Ingredients*
- *Ministerial Ordinance on Quality Assurance of Umbilical Cord Blood for Transplantation*
- *Enhancing the Quality and Safety of Medicines and Medical Devices Using Human-Derived Ingredients and Amendments PFSB No. 0629001 PFSB No. 1213002*
- *The Quality and Safety Assurance of Medicines or Medical Devices Manufactured Using Human (Homogenous)-Derived Cells and/or Tissue FSB Notification No.0912006*

NMPA 

- *Guideline for Chemistry, Manufacturing, and Control (CMC) Studies and Evaluation of Immune Cell Therapy Products (Draft for Comments)*

Regulatory requirements for donor screening and testing vary widely

- Donor screening questionnaire can vary in **timeframe** requirements
- Donor **testing windows** vary across regions
  - Japan
    - Initial: appropriate timeframe
    - Repeat donor testing: shall be performed considering window period
  - US
    - Initial: 7 days, 30 days (bone marrow)
    - Repeat donor testing: not required
  - Europe
    - Initial: 7 days, 30 days (allogeneic bone marrow stem cells or peripheral blood stem cell donor)
    - Repeat donor testing: repeat sampling and serology testing required after 180 days unless living donor undergoes serology testing and molecular testing (HIV, HBC, HCV)
- Infectious disease **testing**
  - US:
    - Must use FDA-approved donor screening assays performed at a CLIA certified lab.
    - Donor eligibility per 21 CFR part 1271 subpart C applies to cells recovered on or after May 25, 2005 (link)
    - Additional viruses: HHV-6, HHV-7, HHV-8, JC virus, BK virus, EBV, Parvovirus B19, HPV, as appropriate (link)

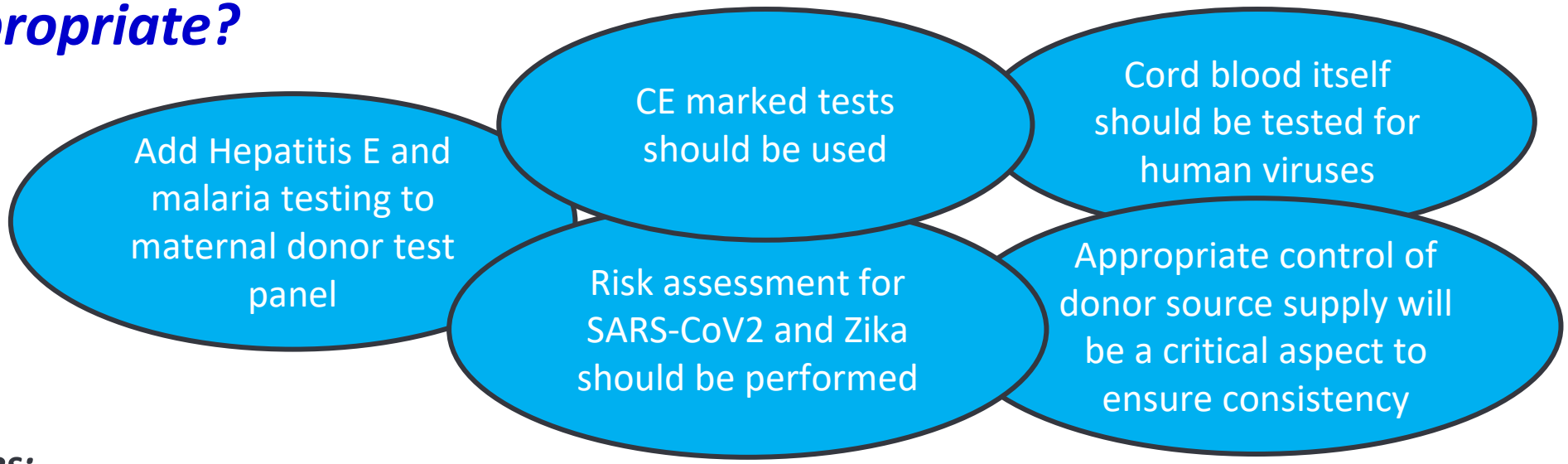
      Strategy for HHV-6
      - Negative lots be released first
      - Positive lots be released in sequence (least to most positive) after sponsor submits preliminary efficacy and safety data in 3-5 subjects who receive negative lots
      - Protocols should mandate assessment and treatment of HHV infections with the onset of neurotoxicity symptoms
  - Europe: CE marked tests (Directive 2006/17/EC, Annex IV) or equivalent at a qualified laboratory

Regulatory requirements for donor screening and testing vary widely

- Risk assessment to identify, evaluate, and mitigate factors that may allow for transmission of ***new emerging pathogens*** that may be relevant for their product
  - Regionally endemic, associated with specific donor populations, or occur during a particular period of time
  - Relevance is based on the risk of transmission, severity of effect, and availability of appropriate screening measures or tests
    - West Nile Virus (WNV), Sepsis, and Vaccinia: not specifically listed under 21 CFR 1271.3(r)(1), were determined to be relevant under 21 CFR 1271.3(r) (2)
    - Zika virus (ZIKV) was a concern from August 2016 under 12 CFR Part 630, but is no longer considered relevant
    - SARS-CoV-2: FDA does not recommend using laboratory tests to screen asymptomatic HCT/P donors since it is not a relevant disease under 21 CFR 1271.3(r). If donor testing for SARS-CoV-2 is incorporated for donor screening as a mitigation strategy, then viral tests (molecular or antigen) approved, cleared, or authorized by the FDA should be used to diagnose current infection
- Other
  - US: Typing for polymorphisms and human leukocyte antigen (**HLA**) matching, where appropriate

CASE STUDY: Cord-blood derived cell therapy product
Pre-CTA Stage; 6 National Health Authorities

General Question: Is specification for the cord blood starting material appropriate?



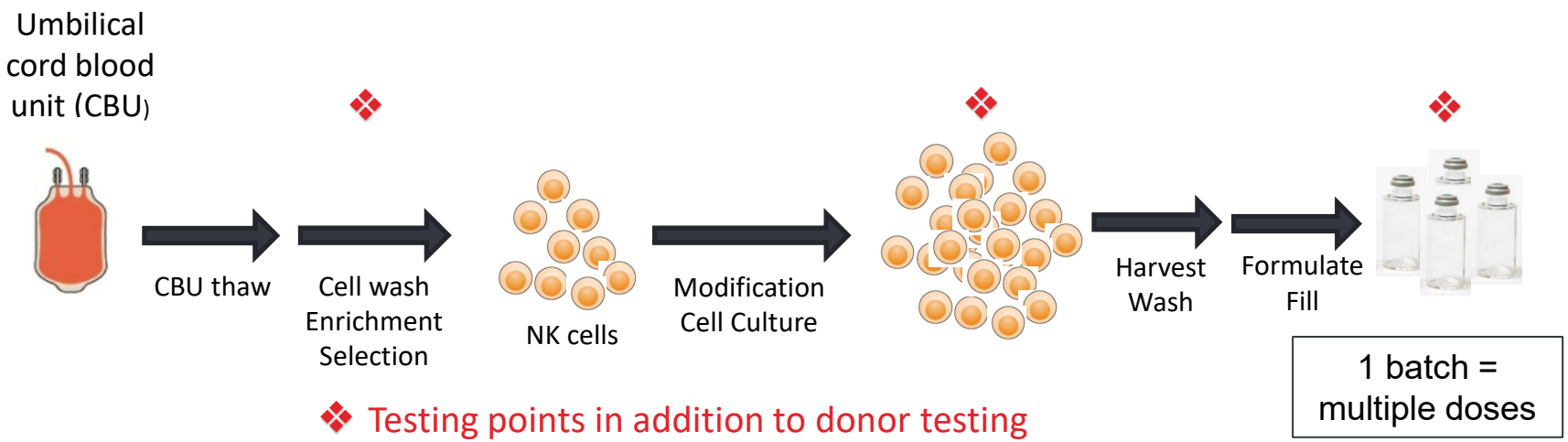
Challenges:

- Cord blood is licensed for allogeneic stem cell transplant. When used as a starting material for cell therapy manufacture, additional controls may apply to mitigate risk from manipulation/expansion of cells.
- Limitations in implementing additional donor screening.
- Volume limitations on material.
- Limitations on how cord blood can be packaged as typically approved in US under BLA (additional aliquots not always available for additional tests).

CASE STUDY: Cord-blood derived cell therapy product
Pre-CTA Stage; 6 National Health Authorities

Proactively obtain regulatory feedback and develop the strategy:

- Test for relevant viruses/infectious diseases in-process and/or at drug product release as opposed to directly in cord blood.
- Work with suppliers for implementing additional donor tests
- Develop supplier questionnaire to ensure global compliance of the starting material for global trials
- Evaluate where may be best to source cells for future supply



Alternative approaches may be possible depending on manufacturing design

- Example: Allogeneic cell therapy where >1000 doses can be manufactured from a single donor source. Cells from multiple donors needed over product life.
  - Regional sourcing to meet regulatory requirements in each region → more complex supply chain
  - Identify testing labs capable of meeting multi-regional requirements

- Example: Allogeneic cell therapy where a single cell from a single donor is used as a source for all cells for the entire product life (e.g. iPSC-derived cells).
  - Identify a new source already reviewed by multiple agencies
  - Identify a new donor and testing labs capable of meeting multi-regional requirements
  - US: File an exemption request and propose an alternative approach for meeting US donor eligibility requirements
  - Other regions: Agency meetings to confirm acceptability

GMP applicability based on manufacturing design

- Vector used to manufacture ex-vivo genetically modified CAR T cells
  - US: Drug Substance, subject to pre-approval inspection
  - EU: Starting material that should follow “Principles of GMP,” GMP certificate not required

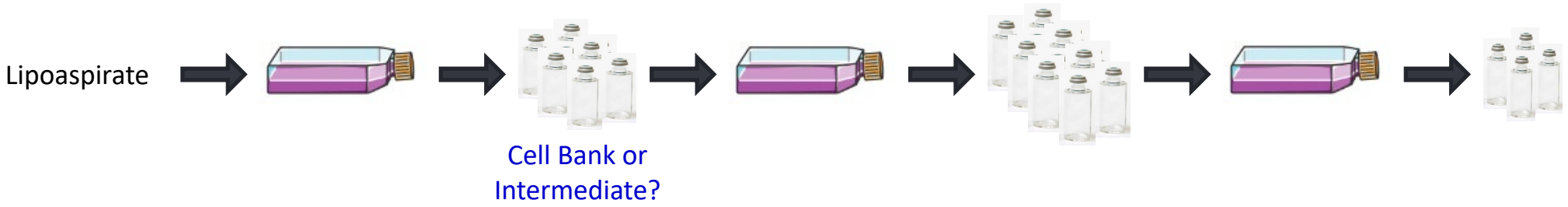
Example Products	Application of GMP to manufacturing steps is shown in dark grey GMP Principles should be applied where shown in light grey **starting material - active substance - finished product** →				
In vivo gene therapy: mRNA	Plasmid, manufacturing and linearization	In vitro transcription		**mRNA** manufacturing and purification	Formulation, filling
In vivo gene therapy: non-viral vector (e.g. naked DNA)	Plasmid manufacturing	Establishment of bacterial bank (MCB, WCB)		**DNA** Manufacturing fermentation and purification	Formulation, filling
In vivo gene therapy: viral vectors	Plasmid manufacturing	Establishment of a cell bank (MCB, WCB) and virus seeds when applicable		**Vector** Manufacturing and purification	Formulation, filling
Ex-vivo: genetically modified cells[3]	Donation, procurement and testing of tissues / cells[1]	Establishment of a cell bank (MCB, WCB) for plasmid and/or vector expansion and viral seeds when applicable	Plasmid manufacturing, Vector manufacturing	**Genetically modified cells** manufacturing	Formulation, filling

In the table above, the AMTP starting materials are underlined and the ATMP active substances appear in bold.
The construction of the plasmid by in silico and molecular biological methods occurs before the plasmid manufacturing and is considered research and development. Therefore it is not under the scope of the current Q&A.

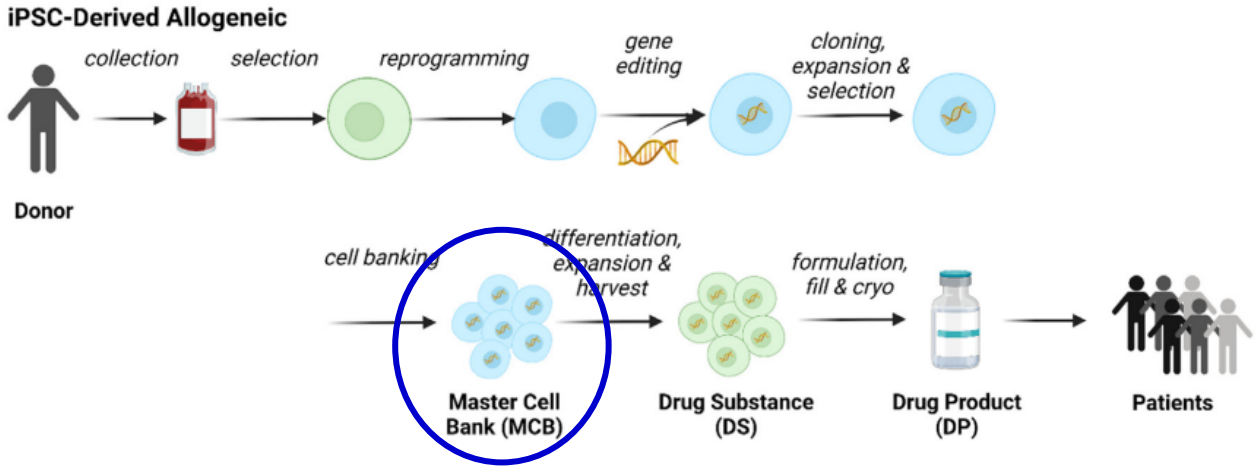
Source: EMA/246400/2021 *Questions and answers on the principles of GMP for the manufacturing of starting materials of biological origin used to transfer genetic material for the manufacturing of ATMPs*

GMP applicability based on manufacturing design

- Non-modified allogeneic cell therapy



- iPSC-derived clonal cell product



Source: Dashnau Jl et al. *A risk-based approach for cell line development, manufacturing and characterization of genetically engineered, induced pluripotent stem cell-derived allogeneic cell therapies.* Cytotherapy. 2022 Sep 12:S1465-3249(22)00746-0. doi: 10.1016/j.jcyt.2022.08.001. PMID: 36109321.

Additional considerations for using allogeneic cells

Key Considerations Prior to Implementing CMAs

Donor-to-Donor Variability	Supply	Development Timing	Comparability

Key Questions

Donor-to-Donor Variability	Supply	Development Timing	Comparability
• Is donor-to-donor-variability well understood for the manufacturing process prior to CMA implementation?	• Is the desired material profile sustainable from a supply standpoint?	• Can the CMA be defined prior to pivotal trials so that the trial is designed to support the hypothesis?	• Can you appropriately demonstrate comparability of the donor-derived material pre- and post-implementation of the CMAs?

Example Strategies

Donor-to-Donor Variability	Supply	Development Timing	Comparability
• Manufacture sufficient lots in early phase studies in order to assess potential effects of donor variability on product. • Hypothesis-based approach to ensure lots manufactured throughout early phase encompass the range of the desired characteristics.	• Work with suppliers on the TPP for donor material. Calculate how restrictive the desired specification could be from a national and global standpoint.	• Early characterization studies inform a list of potential CMAs. • Early clinical studies include sufficient range of batch characteristics to allow identification of potential CMAs/CQAs. • Pivotal trial is powered to test potential CMAs/CQAs.	• When sourcing for new donor cells, it is key to evaluate the ability of the supplier to meet the donor eligibility and testing requirements • Opportunities for discussion with regulators: EOP2/pre-pivotal, pre-comparability, post-comparability, pre-BLA.

Source: Amy McCord, *Control of Allogeneic Donor Cells and Characterization: Integrating into Cell Therapy Regulatory Strategy*, Allogeneic Cell Therapies Summit 2022

CASE STUDY: Adequacy of the potency assay due to complex MoA *remestemcel-L*

Background:

- Mesoblast, Inc. submitted biologics license application (BLA) 125706 seeking to market remestemcel-L, "cellular therapy product composed of allogeneic culture-expanded mesenchymal stromal cells (MSCs) that have been isolated from bone marrow aspirate collected from healthy human donors" for the treatment of "pediatric patients with steroid-refractory acute graft-vs.-host disease."
- A single allogeneic donor → intermediate donor cell bank (DCB) → multiple lots of remestemcel-L drug product
- MSCs in culture cannot expand indefinitely. New DCBs are produced on a regular basis.

Highlights from meeting:

- FDA's position is that the product attributes the Applicant has identified as related to potency and activity, however, do not have a demonstrated relationship to the clinical performance of specific DP lots, and that the product's proposed immunomodulatory mechanism of action has not been demonstrated in vivo in study subjects receiving remestemcel-L. Without a demonstrated relationship with clinical effectiveness and/or in vivo potency/activity, controlling these CQAs may not be sufficient to ensure the manufacturing process consistently produces remestemcel-L lots of acceptable quality.
- Adequacy of the potency assay for maintaining lot-to-lot consistency: The Committee discussed that it was difficult to assess the adequacy of the potency assay due to the complex mechanism of action of remestemcel-L. Another member speculated if whether the existing data, while "imperfect," may be the best available.
- Other possible product quality attributes or characteristics: The Committee noted it is difficult to propose other product quality attributes due to the unclear and complex mechanism of remestemcel-L.

Oncologic Drug Advisory Committee (ODAC) Meeting
Session on Product Characterization (AM Session)
August 13, 2020
https://www.fda.gov/media/140988/download

CASE STUDY: Effect of donor variability on potency
donisclecel

Background:

- CellTrans, Inc. submitted biologics license application (BLA) 125734 seeking to market donislecel, a cellular therapy product composed of allogeneic islets of Langerhans for the treatment of "brittle type I diabetes mellitus (T1D) in adults whose symptoms are not well controlled despite intensive insulin therapy."
- Each lot of donislecel is manufactured from a deceased donor pancreas procured via the Organ Procurement and Transplantation Network (OPTN) and is for the treatment of one patient.

Highlights from meeting:

- Each lot of donislecel is derived from one allogeneic, cadaveric donor pancreas, with each patient receiving up to three lots over the course of their treatment. Inherent variability between donor pancreata contributes to starting material variability. Thus, starting material variability of quality is one of the limitations of the manufacturing process. We ask the Committee to consider the contribution of purity, one of the CQAs, to product safety, efficacy, and manufacturing quality, and discuss whether evaluation of purity and potency is adequate to ensure that the manufacturing process will produce product lots of consistent quality.
- Each dose of donislecel is derived from one deceased donor pancreas. Patients are expected to receive up to three doses to attain the suggested clinical outcomes. Based on data provided from clinical trials, the critical quality attributes are highly variable, and it is not clear how the Applicant achieves lot-to-lot manufacturing consistency in terms of islet purity and potency
- The Committee discussed that it is difficult to have consistent product lots because each lot is derived from a different donor pancreas. In addition, the committee noted that it would be good to have better quality control of the product to avoid administration of multiple doses. The committee suggested adding rapid quality control assays to aid in controlling lot-to-lot variability.

Cellular, Tissue, and Gene Therapies Advisory Committee (CTGTAC) Meeting
Session on Product Characterization (AM Session)
April 15, 2021
https://www.fda.gov/media/147524/download

Summary:

- Understanding the donor selection and testing requirements for regions of interest is critical to ensure compliance of the allogeneic starting material
- GMP applicability of the product should be based on the manufacturing design and product quality controls
- Start characterization early to help understand product potency and donor-to-donor variability

Proactively obtain regulatory feedback and develop the global strategy

Use a risk-based approach for applying GMP

Plan ahead on how to evaluate potency and donor-to-donor variability

Thank you!

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