BE THE MATCH BioTherapies®

Donor Qualification and Procurement of Allogeneic Cellular Starting Material: A Global Regulatory Perspective

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NMDP

National Marrow Donor Program® (NMDP)/Be The Match®

30+ years of global leadership in cell therapy

121,000+ total cell transplants managed

36,000+ annual cell and blood shipments

7,000+ annual cell therapies managed

39+ million donors in the world's most diverse registry

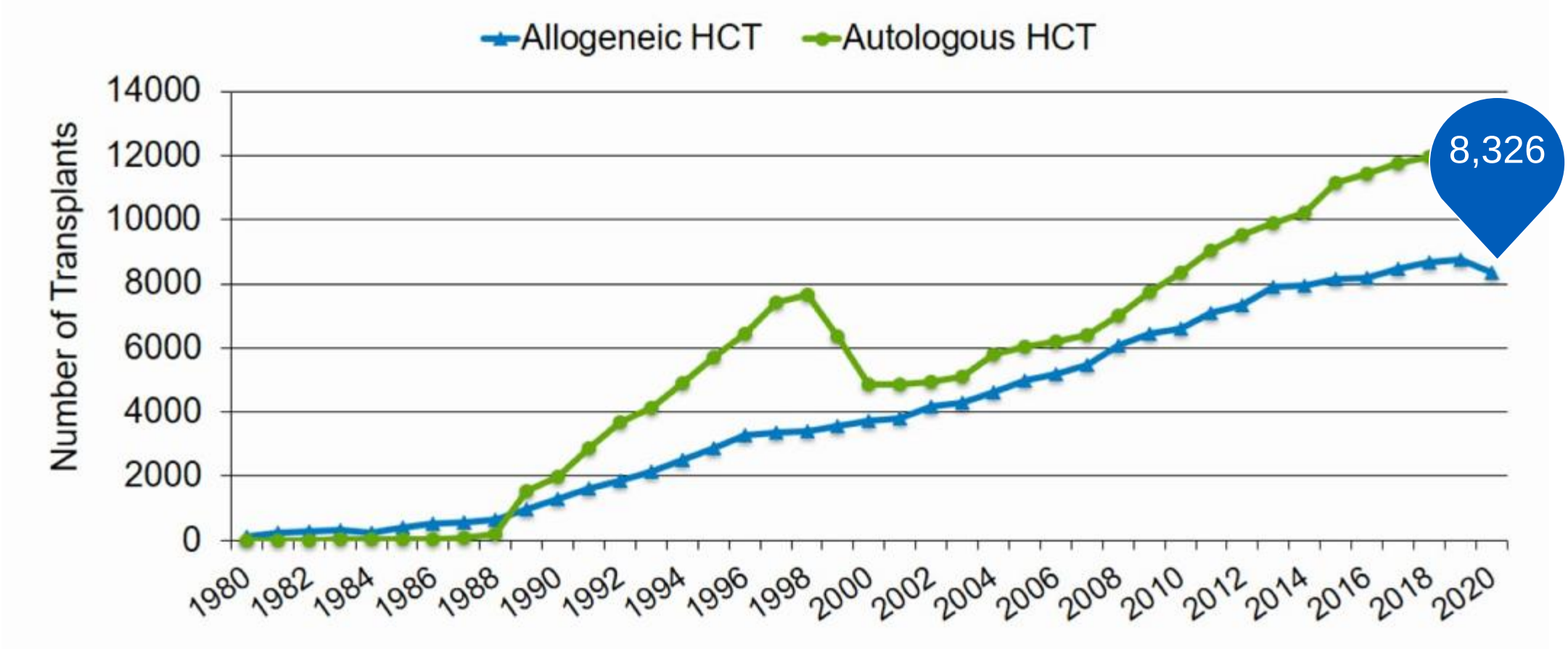
268,000+ cord blood units in domestic banks

225+ research studies underway

1,000+ employees strong

$500+ million annual revenue

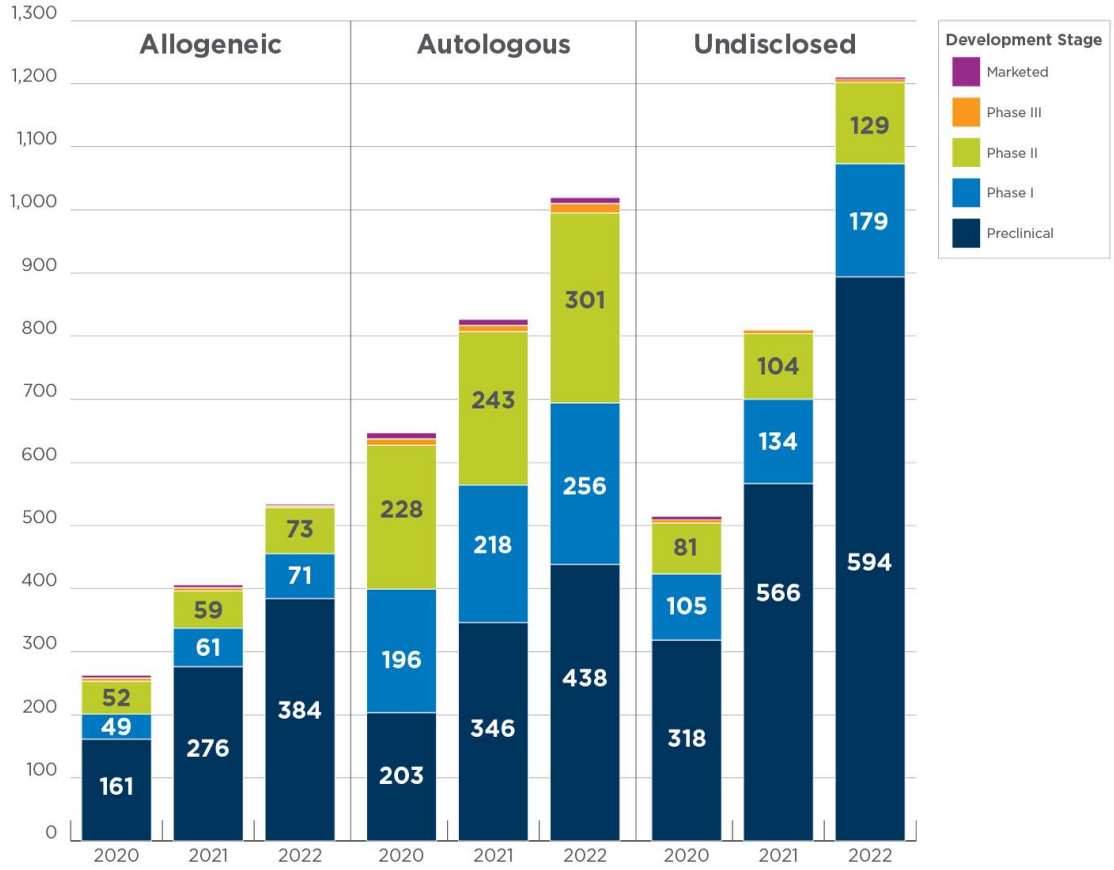
Steady increase in use of hematopoietic stem cell transplant

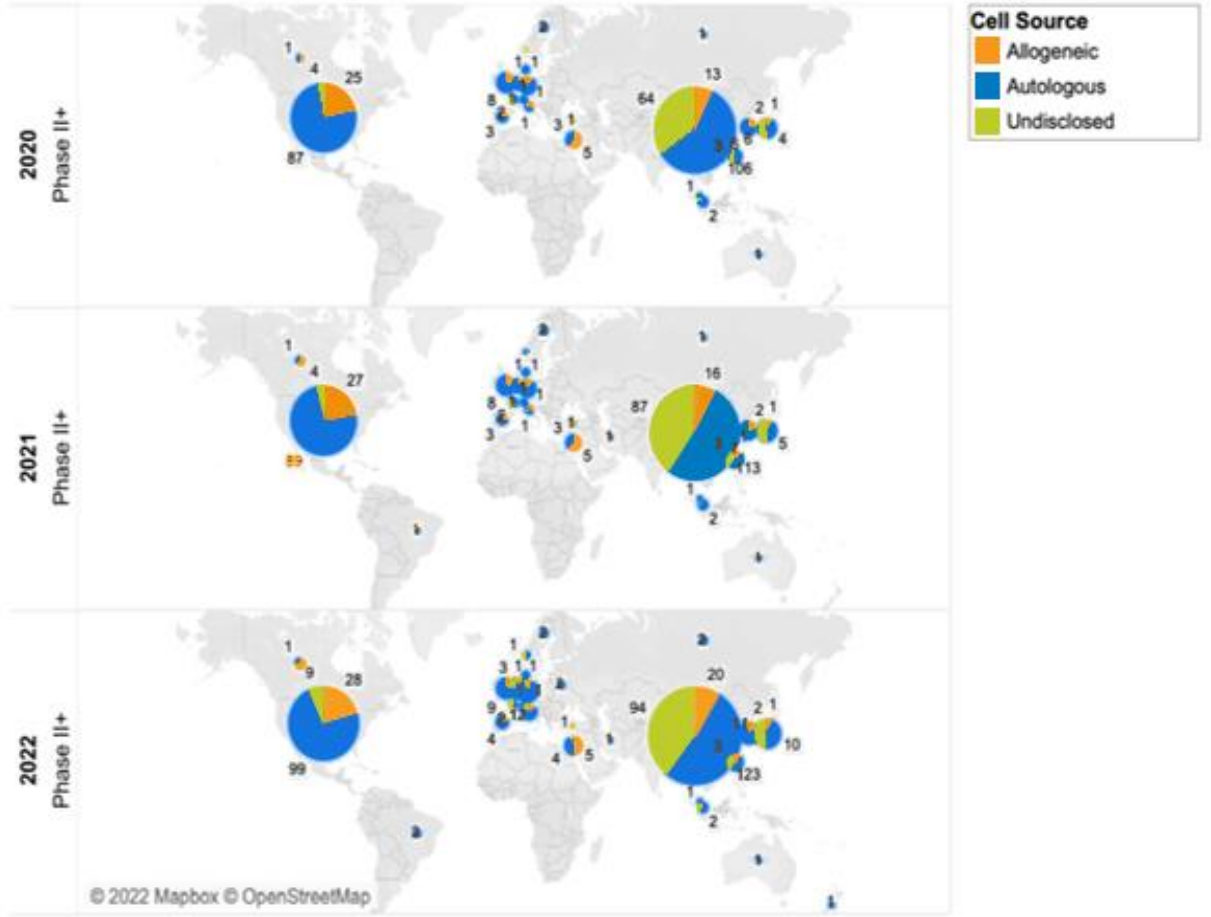


CIBMTR
CENTER FOR INTERNATIONAL BLOOD & MARROW TRANSPLANT RESEARCH

Auletta J.J., Kou J., Chen M., Shaw B.E. **Current use and outcome of hematopoietic stem cell transplantation: CIBMTR summary slides, 2021.** Available at: http://www.cibmtr.org

Growth in Cell & Gene Therapy Sector





Saez-Ibanez, A. et al. Nature Reviews Drug Discovery 2022

Allogeneic Cell Therapy Marketing Authorizations

Adapted from https://alliancerm.org/available-products/

Product	Description	Indication	Market Sector	Region(s)	Year
Apligraf*	Allogeneic foreskin-derived cultured fibroblasts in bovine collagen	Skin ulcers due to venous insufficiency; Diabetic foot ulcers	Wound Healing	USA	2000
Dermagraft*	Allogeneic foreskin-derived cultured fibroblasts in extracellular matrix and bioabsorbable scaffold	Diabetic foot ulcers	Wound Healing	USA	2001
Kaloderm	Allogeneic foreskin-derived keratinocyte cell therapy	Second degree burns; Diabetic foot ulcers	Wound Healing	Rep. of Korea	2005
HPC, CB Products (x7 licensed)	Allogeneic cord blood hematopoietic progenitor cell therapy	Unrelated donor hematopoietic progenitor cell transplantation procedures	HSCT	USA	2011
Cartistem	Allogeneic UCB-derived MSC therapy	Knee cartilage defects/OA/RA	Orthopedics	Rep. of Korea	2012
Gintuit	Allogeneic cultured keratinocytes and fibroblasts in bovine collagen	Mucogingival defects	Wound Healing	USA	2012
TEMCELL	Allogeneic bone marrow-derived MSC therapy	Multiple	Multiple	Canada New Zealand Japan	2012 2012 2015
Keraheal-Allo	Allogeneic keratinocyte hydrogel therapy product	Second degree burns	Wound Healing	Rep. of Korea	2015
Alofisel	Allogeneic adipose-derived expanded stem cell therapy	Complex perianal fistulas in Crohn's Disease	Gastroenterology	EU Japan	2018 2021
Stempeucel	Allogeneic, pooled and expanded adult MSC therapy	Critical Limb Ischemia	Vascular Disorders	India	2020
STRATAGRAFT	Allogeneic dermal cells in murine collagen	Thermal Burns	Wound Healing	US	2021
RETHYMIC	Allogeneic processed thymus tissue-agdc	Immune reconstitution in pediatric patients with congenital athymia	Immunodeficiency	USA	2021
Ebvallo	Allogeneic T-cell immunotherapy	EBV+ PTLD	Hematologic Malignancies	EU	2023
Omisirge-ONLV	Allogeneic NAM-enabled, UCB-derived stem cell therapy	Red. in neutrophil recovery time/infection incidence in UCB transplantation after myeloablative conditioning	Hematologic Malignancies	USA	2023

*Classified as Medical Devices

Healthy Donor Starting Material Cell Sources

Leukapheresis

HPCs[1]
VSTs
T Cell subsets
NK cells
iNKT Cells

Cord Blood

HPCs
Monocytes
Lymphocytes
Granulocytes

Tissue

Bone Marrow[2]
Foreskin
Adipose
Placenta
Skin

1. G-CSF mobilization required
2. May be regulated as a different product class across geographies

Opportunities By Cell Source

Leukapheresis

- Specification development to fit TPP
- Screening/testing can be done prospectively
- Volume/concentration manipulations are possible
- Avoidance of cryopreservation

Cord Blood

- Readily available
- HLA typed
- Screened/tested donors
- Sterility results on file

Tissue

- Potential decreased need for manipulation
- Availability of both living and cadaveric sources
- Robust clinical infrastructure for tissue procurement

Challenges By Cell Source

Leukapheresis

- Donor to donor variability
- Complex logistics/supply chain
- Coordination of donation with manufacture

Cord Blood

- Limitations on retrospective screening/testing
- Availability of samples/segments for additional assessments
- Volume limitations
- Viability due to freeze/thaw

Tissue

- Isolation/disaggregation
- Availability of cadaveric screening tests
- Manufacturing consistency data can be difficult to establish for 1:1 donor:patient ratio

CMA/CQA Definition for Starting Materials Can Be Challenging

Consider the…

Cell Source	Level of Donor Assessment	Level of Manipulation/ Processing	Intended Patient Population	Manufacturing Method
Are reference standards available?	Serology and NAT assessment performed?	Cellular selection and/or enrichment?	Level of immunocompetency	Transduction efficiency
Source-specific guidance provided by applicable Authorities?	Genetic sequencing?	Significant exposure to raw materials during processing?	Geographic location (transport/logistics constraints)	Differentiation potential
Precedent for similar authorized modality?	Detailed family history available?	Scalable/sustainable from supply chain perspective?	Age/BMI/Disease Burden	Expansion capability
	Phenotypic screening for manufacturing permissivity?	Fresh vs Cryo'd?	HLA matching (if applicable)	Comparability between donors?
		In-process sterility?		

CMA/CQA Definition for Starting Materials Can Be Challenging

Potential CMA/CQAs may be informed by …

Cell Source	Level of Donor Assessment	Level of Manipulation/ Processing	Intended Patient Population	Manufacturing Method
Donor Eligibility/Suitability	Donor requirements (Sex, Age, HLA type, immune history, SNPs)	Pre/post-processing recovery	Latent infection status (CMV, EBV, HHV6/7)	Phenotypic screening performance
Phenotypic parameters	Karyotype	In-process sterility	HLA Matched/Partially Matched/Mismatched	Growth/culture metrics
Genotypic parameters	Genetic risk loci	In-process AVT	ABO/Rh	Transgene expression
Starting Material CBC/TNC/TVNC	Genetic stability			MoA
State (Fresh/Cryo'd)				Contamination

- **Characterization studies should be emphasized in early development with comprehensive data capture based on risk assessment, scientific rationale and availability of appropriate assays**
- **Future correlation to manufacturing yield, functional Product characteristics and ultimately clinical safety and efficacy require casting of a wide net early in process development to ensure CMAs/CQAs can be identified/established in later phases on development**

Key Regulations & Guidances for Donor Eligibility of Cellular Starting Materials Across Geographies

USA | FDA

21 CFR 1271

- Guidance for Industry: Eligibility Determination for Donors of HCT/Ps (2007)
- Guidance for Industry: CMC Info for Human Gene Therapy IND Applications (2020)
- DRAFT Guidance for Industry: Considerations for the Development of CAR-T Cell Products (2022)

EU | EMA

2004/23/EC
2006/17/EC

- Guideline on Human Cell-based Medicinal Products (2008)
- Scientific Guideline on Stem-Cell Based Medicinal Products

Australia | TGA

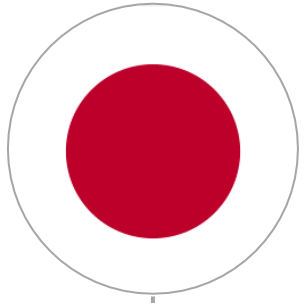
TGO 108
TGO 109

- ARGB Appx 12-Guidance on TGO 108: Standard for Human Cell or Tissue Products - Donor Screening Requirements
- ARGB Appx 13 – Guidance on TGO 109: Standard for Biologicals – General and Specific Requirements

Canada | HC

CAN-CSA-Z900.1.22
CAN-CSA-Z900.2.5.22

- Guidance Document for Cell, Tissue and Organ Establishments - Safety of Human Cells, Tissues and Organs for Transplantation



Japan | PMDA MHLW

MHLW No. 0907-3
MHLW No. 375

- Guidelines on Ensuring the Quality and Safety of Pharmaceuticals and Medical Devices Derived from the Processing of Allogeneic Human Somatic Stem Cells (2012)

Korea | MFDS

Regulation on Approval and Review of Biological Products

- Guideline on Eligibility Determination for Donors of Cell Therapy Products (2016)
- Guideline on Assessment of Stem Cell Products (2014)

Recent/Proposed Guidance of Note

FDA

- Draft Guidance for Industry (CBER Guidance Release Agenda 2023)
  - Safety Testing of Human Allogeneic Cells Expanded for Use in Cell-Based Medical Products; Draft Guidance for Industry (**Release date TBD**)
  - Recommendations for Determining Eligibility of Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps); (**Release date TBD**)
  - Manufacturing Changes and Comparability for Human Cellular and Gene Therapy Products; Draft Guidance for Industry (**Release date TBD**)

TGA

- Update to the Manufacturing Principles for medicines, APIs & sunscreens
  - PIC/S Guide to Good Manufacturing Practice for Medicinal Products (PE009-15) (**Jul 2022**)

Health Canada

- Draft Guidance on Advanced Therapeutic Products Framework: Overview (**Dec 2022**)

WHO

- Draft whitepaper: WHO approach towards the development of a global regulatory framework for cell and gene therapy products (BS2022.2424) (**2022**)

Highly Variable Eligibility Requirements Across Geographies

- **Screening Timeframe**
- Screening Requirements
- Sampling Timeframe
- Testing Requirements
- Best Practices

- Performance timeframe undefined in many regions while explicitly defined in others; Assessments should match most restrictive timeframes when feasible
  - Ex. TGA requires interview performed +/- 30 days from time of recovery
- Review and/or re-administration of screening advisable at the time of donation if performed in advance; mechanism for notification of donor changes and review of impacts prior to product release

Highly Variable Eligibility Requirements Across Geographies

- Screening Timeframe
- **Screening Requirements**
- Sampling Timeframe
- Testing Requirements
- Best Practices

- Highly region-specific; Generally focus on:
  - Communicable disease risks
  - Medical, social and family history
  - Environmental exposures; Travel
  - Physical Examination
- Training/qualification requirements for staff performing screening activities in some cases are explicitly defined; contractual considerations in some circumstances
- Biovigilance considerations
- Recommend detailed Gap Analysis of requirements across desirable markets

Highly Variable Eligibility Requirements Across Geographies

Screening Timeframe

Screening Requirements

Sampling Timeframes

Testing Requirements

Best Practices

- Timeframes for sampling likewise vary
  - USA: Time of recovery or +/- 7 days[1]
  - EU: Time of recovery or 7 days post-recovery; repeat 180 days post-recovery[2]
  - AUS: Time of recovery or +/- 7 days
  - CAN: Within 30 days prior to recovery
  - JAP: Appropriate timeframe; Repeat post-recovery with window period
  - KOR: Time of recovery or 7 days post-recovery
- Archival sample considerations
- Cadaveric requirements may differ from living donor requirements

1. Donors of HSCs (HPC(A); HPC(M) as applicable) can be sampled within 30 days prior or up to 7 days post-recovery to account for coordination of patient conditioning regimens (also assists with scheduling and performance of G-CSF mobilization)
2. Not required for living donors if serological and molecular testing for HIV, HBV and HCV is performed at the time of recovery or 7 days post-recovery

Highly Variable Eligibility Requirements Across Geographies

- Screening Timeframe
- Screening Requirements
- Sampling Timeframe
- **Testing Requirements**
- Best Practices

- USA: FDA licensed/approved/cleared donor screening tests (where available) tested in a CLIA certified laboratory
- EU: CE-marked test kits; GMP certificate for donor testing may be required by NCAs
- CAN: Licensed (HC/FDA) test kits (where available) in qualified laboratories;
- AUS: IVDs (Registered; or approved by Int'l NCA) in TGA cleared facility
- JAP: appropriate according to latest findings about infectious diseases
- KOR: IVDs or appropriately validated methods in a diagnostic facility or hospital laboratory with demonstrated QC

Highly Variable Eligibility Requirements Across Geographies

- Screening Timeframe
- Screening Requirements
- Sampling Timeframe
- Testing Requirements
- **Best Practices**

- Assess regulatory requirements of potential markets of interest early and in detail to understand key regional differences; Use most restrictive requirements and work backwards
- Develop screening questionnaire(s) that assess for risks across geographies and account for travel risks
- Identify laboratories capable of meeting testing requirements of multiple regions (where feasible); identify back-up labs for risk reduction
- Consider feasibility/appropriateness of archival PB samples
- Engage Authorities for feedback whenever feasible prior to implementation of Specifications

Infectious Disease Assessments By Region

Pathogen	USA	EU	AUS	CAN	JAP	KOR
HIV1	X	X	X	X	X	X
HIV2	X	X	X	X	X	X
HBV	X	X	X	X	X	X
HCV	X	X	X	X	X	X
T. Palladium	X	X	X	X	X	X
HTLV I/II	X	X	X	X	X	X
CMV	X	X	X	X	X	X
TSE/CJD	X		X	X	X	X
Zika	X		X	X		X
Ebola		May require assessment	X	X		X
West Nile Virus	X	X		X		
Parvo B19	May require assessment	X			X	
Malaria		?	X	X		
T. cruzi (Chagas)	X			X		
Toxoplasma		X			X	
EBV	May require assessment	May require assessment			X	
Dengue			X	X		
Chlamydia	X				X	
N. gonorrhoeae	X				X	
Vaccinia	X	May require assessment				
Rabies				X		
HEV		X				
HAV		X				
SARS-CoV-2	May require assessment		May require assessment			
M. tuberculosis					X	
HHV 6/7/8	May require assessment					
HSV I/II	May require assessment					
JC Virus	May require assessment					
BK Virus	May require assessment					
HPV	May require assessment					

NOTE: Above table does not differentiate between screening versus testing; screening and/or testing of pathogens may be required depending on Authority

Highlighted Testing/Screening Considerations

- FDA TSE/CJD screening requirements generally render EU donors ineligible for donation
- Japan recommends avoidance of donors from specific countries; risk assessment and context-appropriate rationale should be developed if sourcing of donors from such countries
- Additional and/or repeat testing may be required based on regional requirements (IE Germany/PEI);
- Import re-testing may be required for internationally-sourced material if inappropriate kits or unqualified labs are utilized for original eligibility assessments
- Positive/indeterminant results in one region's eligibility can impact eligibility of other regions
- Many Authorities specify requirements for appropriate retain samples for emerging infectious disease risk mitigation
- Serological assessment of common viral infections (CMV, EBV, HHV6/7/8) may drastically limit donor pools; justification of test methods and screening criteria should be documented and assessed based on risks;
    - IgM and/or NAT assessment of donors could be considered, with appropriately qualified/validated testing of DP prior to release
- Non-IDM testing requirements may include:
    - ABO/Rh, Rh-D, RBC Antibodies, HLA, etc

Donor Informed Consent

- Consent requirements exist across all major markets; some explicitly defined in regulations, others less defined
- Donor research subject determination is critical to ensuring appropriate protections and elements of informed consent are performed and documented
- Specificity of consent should align with knowledge of intent for use of donated material; Re-consenting of donors should be evaluated if intent/context/knowledge changes
- Altruistic voluntary donation generally favored across geographies; Many Authorities prohibit use of material from compensated (but not necessarily reimbursed) donors
- WMDA, FACT/JACIE, FACT/Netcord and AABB accreditations likewise hold consent requirements.
- Identify unique requirements for consent across geographies and incorporate into collection consents (or determine feasibility of re-consent of donors for banked material)

Case Study: FDA Complete Response Letter highlights potency assay and manufacturing consistency concerns for RETHYMIC

- Enzyvant submitted BLA 125685/0 in April 2019 to market RETHYMIC, an allogeneic cell therapy product derived from unrelated donor thymus tissue; indicated for immune reconstitution in pediatric patients with congenital athymia
- Thymus tissue isolated from a single donor (donors are patients undergoing heart surgery) and cultured for 12-21 days to produce a single lot of RETHYMIC intended for a single patient (1:1 donor to patient ratio)
- Potency assay utilized for original BLA submission was composed of a qualitative histological readout for cytokeratin and CD3+ thymocyte expression and localization (in additional to generalized histological assessment of thymus architecture
- Complete Response Letter issue by FDA in Dec 2019 highlighting CMC concerns regarding the potency assay utilized for RETHYMIC
  - FDA took position that process validation inadequately demonstrated manufacturing and product consistency for all required elements
  - FDA expressed concerns regarding wide variation seen in the phenotype of the donor-derived tissue and the lack of specificity of the histological assay and its acceptance criteria; Made assessment of manufacturing consistency between lots challenging
  - Additional concerns regarding lack of retrospective data analysis of quality measures of product lots received by patients who experienced positive versus negative/delayed outcomes
- Type A meeting held Mar 2020 to discuss Enzyvant approach to resolving deficiencies described in CRL
  - Ultimately, histological potency assay was modified from qualitative to semi-quantitative and additional histological data on clinical lots was submitted
  - Retrospective quality assessment of clinical lots performed in 29 patients with delayed naïve T cell elevation; no significant difference found in properties of lots for these patients
- RETHYMIC BLA resubmitted Apr 2021 with Approval occurring in Oct 2021 following FDA stance that all described deficiencies were adequately addressed

FDA RETHYMIC Complete Response Letter - 04Dec2019
https://www.fda.gov/media/153874/download

FDA RETHYMIC Summary Basis for Regulatory Action – 08Oct2021
https://www.fda.gov/media/153729/download

Summary

Regulatory requirements for donor qualification and eligibility determination are highly variable across Authorities; detailed assessments of inter-Authority differences are critical to ensuring compliance with requirements of desired markets

CMA/CQAs are challenging to define for allogeneic cell therapy starting materials; great care should be taken to ensure adequate data capture in starting material attributes during early development phases to permit comparability assessment of donor-to-donor variation, for later manufacturing process optimization, and for eventual correlation of attributes to clinical safety and efficacy outcomes.

At all stages of development, a risk-based approach should be emphasized along with proactive Authority engagement for feedback on approach and determination of acceptability, especially in contexts without previous MA precedent

Thank you!

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