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

Growth in Cell & Gene Therapy Sector

# Allogeneic Cell Therapy Marketing Authorizations

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

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

*Classified as Medical Devices
Healthy Donor Starting Material Cell Sources

Leukapheresis
- HPCs
- VSTs
- T Cell subsets
- NK cells
- iNKT Cells

Cord Blood
- HPCs
- Monocytes
- Lymphocytes
- Granulocytes

Tissue
- Bone Marrow
  - 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…

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

Potential CMA/CQAs may be informed by …

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

- 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
<table>
<thead>
<tr>
<th>Geography</th>
<th>Key Regulations &amp; Guidances</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA</td>
<td>21 CFR 1271</td>
</tr>
<tr>
<td>EU</td>
<td>2004/23/EC 2006/17/EC</td>
</tr>
<tr>
<td>Australia</td>
<td>TGO 108 TGO 109</td>
</tr>
<tr>
<td>Canada</td>
<td>CAN-CSA-Z900.1.22 CAN-CSA-Z900.2.5.22</td>
</tr>
<tr>
<td>Japan</td>
<td>MHLW No. 0907-3 MHLW No. 375</td>
</tr>
<tr>
<td>Korea</td>
<td>Regulation on Approval and Review of Biological Products</td>
</tr>
</tbody>
</table>

- Guidance for Industry: Eligibility Determination for Donors of HCT/Ps (2007)
- DRAFT Guidance for Industry: Considerations for the Development of CAR-T Cell Products (2022)
- Guideline on Human Cell-based Medicinal Products (2008)
- Scientific Guideline on Stem-Cell Based Medicinal Products
- 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
- Guidance Document for Cell, Tissue and Organ Establishments - Safety of Human Cells, Tissues and Organs for Transplantation
- Guidelines on Ensuring the Quality and Safety of Pharmaceuticals and Medical Devices Derived from the Processing of Allogeneic Human Somatic Stem Cells (2012)
- 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

- 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

- 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

- **Sampling Timeframes**
  - **Screening Timeframe**
  - **Screening Requirements**
  - **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**

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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

<table>
<thead>
<tr>
<th>Screening Timeframe</th>
<th>Screening Requirements</th>
<th>Sampling Timeframe</th>
<th>Testing Requirements</th>
<th>Best Practices</th>
</tr>
</thead>
<tbody>
<tr>
<td>• USA: FDA licensed/approved/cleared donor screening tests (where available) tested in a CLIA certified laboratory</td>
<td>• EU: CE-marked test kits; GMP certificate for donor testing may be required by NCAs</td>
<td>• CAN: Licensed (HC/FDA) test kits (where available) in qualified laboratories;</td>
<td>• AUS: IVDs (Registered; or approved by Int'l NCA) in TGA cleared facility</td>
<td>• JAP: appropriate according to latest findings about infectious diseases</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• KOR: IVDs or appropriately validated methods in a diagnostic facility or hospital laboratory with demonstrated QC</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Highly Variable Eligibility Requirements Across Geographies

- 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

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>USA</th>
<th>EU</th>
<th>AUS</th>
<th>CAN</th>
<th>JAP</th>
<th>KOR</th>
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<tbody>
<tr>
<td>HIV1</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<td>HIV2</td>
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<td>X</td>
<td>X</td>
<td>X</td>
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<td>HBV</td>
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<td>X</td>
<td>X</td>
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<tr>
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<td>X</td>
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<tr>
<td>T. Palladium</td>
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<td>X</td>
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<td>HTLV I/II</td>
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<td>X</td>
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<td>CMV</td>
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<td>West Nile Virus</td>
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<td>Parvo B19</td>
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<td>Malaria</td>
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<td>T. cruzi (Chagas)</td>
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<td>May require assessment</td>
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<td>EBV</td>
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<td>Dengue</td>
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<td>Chlamydia</td>
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<td>N. gonorrhoeae</td>
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<td>Vaccinia</td>
<td>May require assessment</td>
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<tr>
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<td>SARS-CoV-2</td>
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<td>M. tuberculosis</td>
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<td>HHV 6/7/8</td>
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<td>HSV I/II</td>
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<td>X</td>
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<tr>
<td>JC Virus</td>
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<td>BK Virus</td>
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<td>HPV</td>
<td>May require assessment</td>
<td>May require assessment</td>
<td>X</td>
<td></td>
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</tr>
</tbody>
</table>

**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 addition to generalized histological assessment of thymus architecture)
- Complete Response Letter issued 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!