# Advanced Therapy Medicinal Products – Medicines and Biologicals

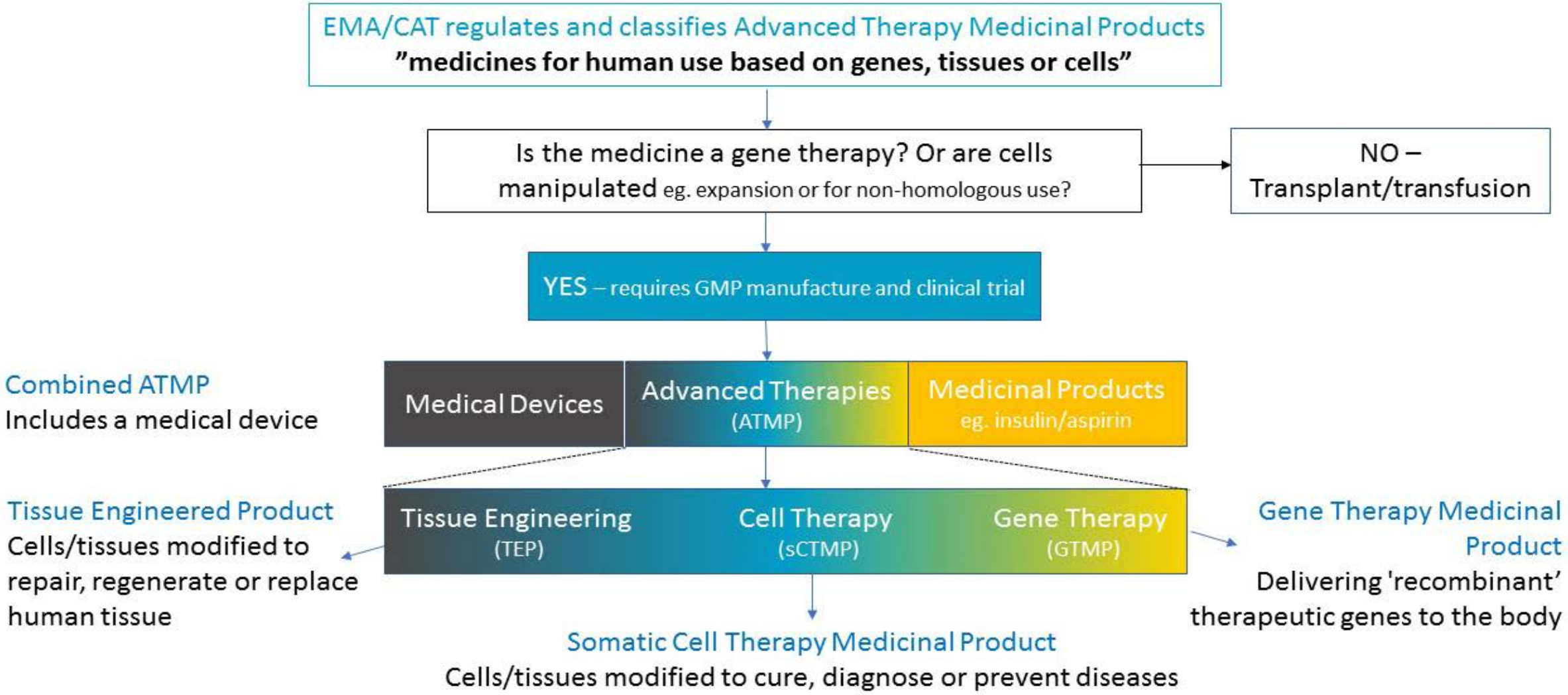
Amanda Louise and Fran Harding
Manufacturing Quality
Department of Health and Aged Care, TGA

GMP FORUM 2024

# Agenda

- What is an ATMP?
- Types of ATMPs
- Regulatory framework
- Applications
- Challenges with ATMPs
- Inspection insights
- Future Perspective

# What is an ATMP?



# Types of ATMPs

## 4 Categories of (ATMPs) according to the European Medicines Agency (EMA) and the Medicines and Healthcare Products Regulatory Agency (MHRA)

| | | | |
|---|---|---|---|
|  | **Tissue-engineered therapies** | administered to human beings with a view to “regenerate, repair or replace a human tissue”. | Skin grafts, e.g. Stratagraft. |
|  | **Somatic cell therapies** | substantially manipulated and “contain or consist of engineered cells or tissues” administered with a view to “treat, prevent, or diagnose a disease through pharmacological, immunological, or metabolic action on cells or tissues” | CAR-T Cell Therapies, e.g. Yescarta. |
|  | **Gene-therapy medicinal products** | “biological products with an active substance which contains a recombinant nucleic acid with a view to regulate, repair, replace, add, or delete a genetic sequence and that will have a therapeutic, prophylactic or diagnostic effect on the patient.” Gene therapies do not include vaccines. | Replace an abnormal gene with a normal gene, e.g. Zolgensma. |
|  | **Combined ATMPs** | “incorporate an active substance”, that is, a cellular or tissue part consisting of viable or non-viable cells or tissues in addition to “one or more medical devices or active implantable medical devices as an integral part of the product”. | Cells embedded in a biodegradable matrix or scaffold, including 3D printing E.g. hHVS Heart Valves. |

Source: https://doi.org/10.1016/j.drudis.2023.103549

# Australian Definitions

The Australian regulatory frameworks make a distinction between biologicals and biological medicines.

## Biologicals

A thing made from, or that contains, human cells or human tissues, and that is used to:

- treat or prevent disease, ailment, defect or injury
- diagnose a condition of a person
- alter the physiological processes of a person
- test the susceptibility of a person to disease
- replace or modify a person's body parts

and

- a thing that is a faecal microbiota transplant product
- a thing that comprises or contains live animal cells, tissues or organs

## Biological Medicines

A medicine (other than an antibiotic) that is:

- a vaccine, a peptide, a protein, a polysaccharide; and
- derived from a human, animal or other organism, or produced through recombinant technology or biotechnology; and
- of a kind specified in item 1 of Part 1 of Schedule 10 (includes biotechnology medicines);
- but does not include a 'biological' within the meaning of section 32A of the Therapeutic Goods Act 1989 (the Act).

# Australian Guidelines

## Overview of Australian Regulatory Guidelines for Biologicals

- The Australian Regulatory Guidelines for Biologicals (ARGB) provide a framework for regulating the majority of biological products. It outlines the processes for assessing the quality, safety, and efficacy of biological medicines.
- Biologicals include products derived from human cells or tissues, and guidelines ensure compliance with Good Manufacturing Practice. Australian Code of GMP for Human Blood and Blood Components, Human Tissues and Human Cellular Therapy Products 2013 applies
- E.g. tissue-based products, cell-based products, immunotherapy products containing human cells, autologous human cells and tissue products (including stem cells), gene-modified cell therapies.
- GMP certificates are issued by TGA for overseas sites (GMP clearance for Sponsor) This includes sites that conduct donor testing and release testing of biological product

## Overview of Prescription Medicines Guidelines

- The Australian Regulatory Guidelines for Prescription Medicines (ARGPM) set standards for the registration of prescription medicines.
- It emphasizes quality control, safety, and efficacy, following a risk-based approach to evaluation.
- Both ARGB and ARGPM are critical for ensuring public health and safety in the use of therapeutic goods. PIC/S Guide to Good Manufacturing Practice (GMP) for medicinal products applies.
- E.g. recombinant products, plasma derived products (or that contain plasma derived products), vaccines (that do not contain viable human cells), gene-therapy vectors alone.
- GMP clearance pathway (API, MRA pathways) exist for biological medicines.

# PIC/S Annex 2A

*For ATMPs, which cover cell and gene therapy products.*
***Part A** - control over seed lots and cell banks through to finishing activities and testing*
***Part B** - more specific guidance on selected product types, such as animal sourced products and gene therapy products.*

Revisions aim to:

- Accommodate key challenges such as “diffuse manufacturing”.
- Facilitate cross border movement of ATMP.
- Bridge cross all the expectations for these products through all jurisdictions, even the countries that may not formally adopt it.

Flexibility exists in the guidance due to breadth and diversity of products covered.
Different design approaches are possible.

Considers the starting materials, ATMP active substance and finished ATMP
Noting that: the manufacturing process between ATMP active substance and the final product can be continuous.

The manufacture and control of genetically modified organisms also needs to comply with other local, national or regional requirements (OGTR in Australia)

# Knowledge Check

For the following products, are they a Biological or Biological Medicine?

1. Yescarta
2. Faecal microbiota transplant (FMT)
3. Zolgensma

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# Biological or Biological Medicine?

## Yescarta

Yescarta (axicabtagene ciloleucel) is classified as a Biological.
It is a CAR T-cell therapy used for the treatment of certain types of lymphomas.

## Faecal Microbiota Transplant (FMT)

Faecal microbiota transplant (FMT) is classified as a Biological.
In Australia, it is recognized under Biological Class 1 or 2.

## Zolgensma

Zolgensma (onasemnogene abeparvovec-xioi) is classified as a Biological medicine. It is a gene therapy for spinal muscular atrophy (SMA) and involves the delivery of a functional copy of the SMN1 gene.

# Knowledge Check

The Australian code of good manufacturing practice for human blood and blood components, human tissues and human cellular therapy products V1.0 was introduced in April 2013.

As of today, how many Biological products are registered on the ARTG?

1. Less than 10
2. 10 – 20
3. 30 – 60
4. 60 - 100
5. More than 100

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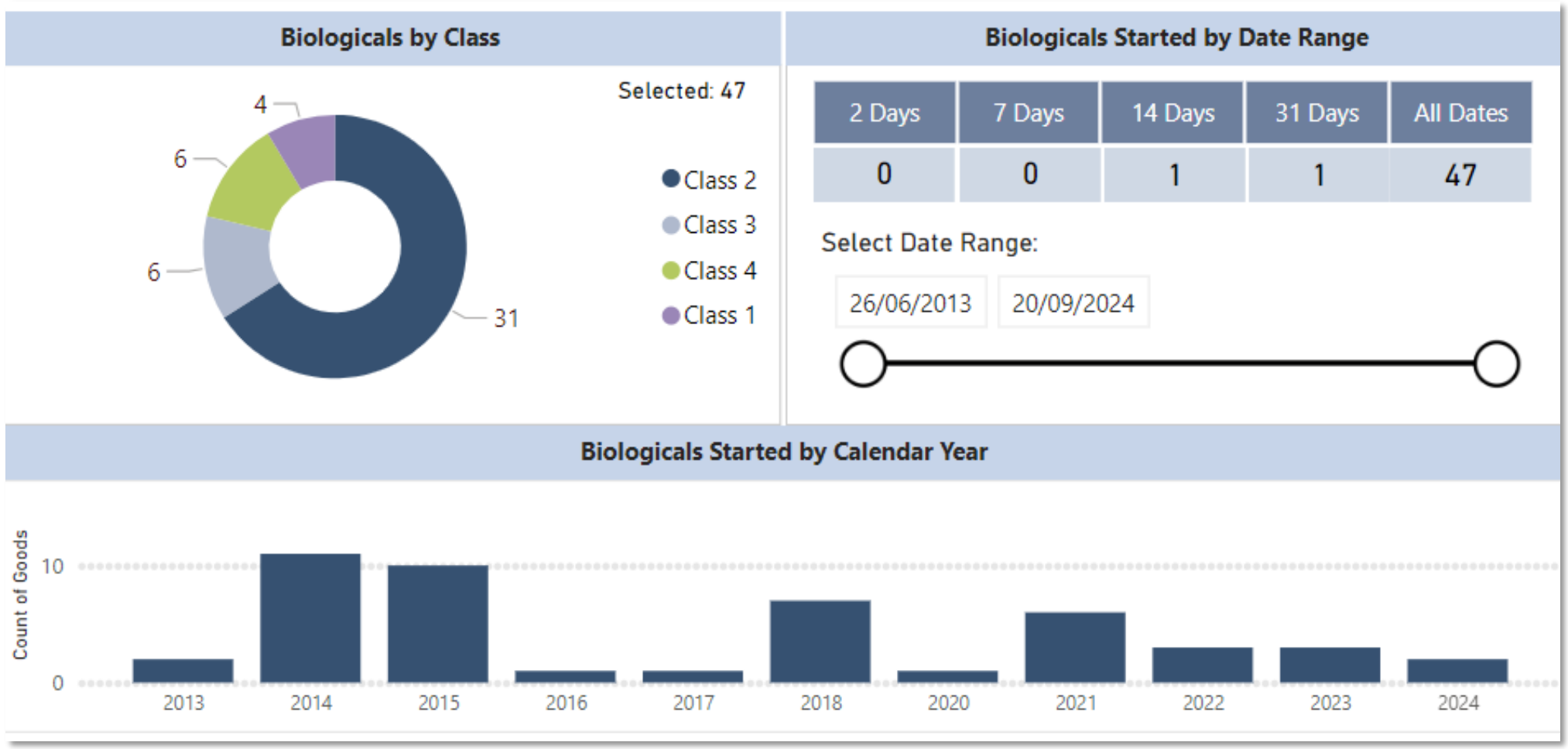
# Biologicals




Search result: 47 ARTG entries

Source: https://compliance.health.gov.au/artg

# Six Class 4 Biologicals approved on ARTG

| ARTG ID | Sponsor Name | Product Name | Approval Area | Product Type | Therapeutic Indication |
|---|---|---|---|---|---|
| 400895 | Gilead Sciences Pty Ltd | T Cells - Axicabtagene ciloleucel, cryopreserved - T - Yescarta | Biologicals | Cellular Therapies | YESCARTA is a genetically modified autologous immunocellular therapy for the treatment of:Large B-cell Lymphoma. |
| 371431 | Gilead Sciences Pty Ltd | T Cells - Brexucabtagene autoleucel, cryopreserved - T - Tecartus | Biologicals | Cellular Therapies | TECARTUS is a genetically modified autologous immunocellular therapy for the treatment of patients with relapsed or refractory mantle cell lymphoma (MCL), who have received two or more lines of therapy, including a BTK inhibitor, unless ineligible or intolerant to treatment with a BTK inhibitor. |
| 396794 | Gilead Sciences Pty Ltd | T Cells - Brexucabtagene autoleucel, cryopreserved - T - Tecartus | Biologicals | Cellular Therapies | TECARTUS is a genetically modified autologous immunocellular therapy for the treatment of patients greater than or equal to 18 years of age with relapsed or refractory (r/r) B-cell acute lymphoblastic leukaemia (B-ALL). |
| 312685 | Novartis Pharmaceuticals Australia Pty Ltd | T Cells - Tisagenlecleucel, cryopreserved - T - Kymriah | Biologicals | Cellular Therapies | Kymriah is a genetically modified autologous immunocellular therapy indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) after two or more lines of systemic therapy. |
| 312686 | Novartis Pharmaceuticals Australia Pty Ltd | T Cells - Tisagenlecleucel, cryopreserved - T - Kymriah | Biologicals | Cellular Therapies | Kymriah is a genetically modified autologous immunocellular therapy indicated for the treatment of paediatric and young adult patients up to 25 years of age with B-cell precursor acute lymphoblastic leukaemia (ALL) that is refractory, in relapse post-transplant, or in second or later relapse. |
| 410143 | Janssen-Cilag Pty Ltd | T cells-Ciltacabtagene autoleucel, cryopreserved-T-CARVYKTI | Biologicals | Cellular Therapies | CARVYKTI is indicated for the treatment of adult patients with relapsed or refractory multiple myeloma, who have received at least three prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 antibody. |

# Knowledge Check

How many Licensed Biological Products registered with the FDA?

1. Less than 200
2. Between 200 and 1000
3. Over 1000

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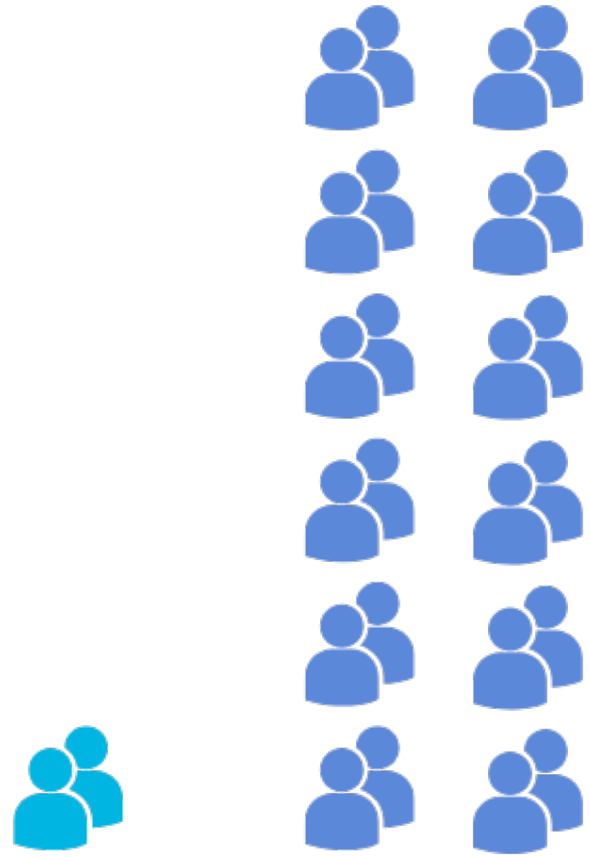
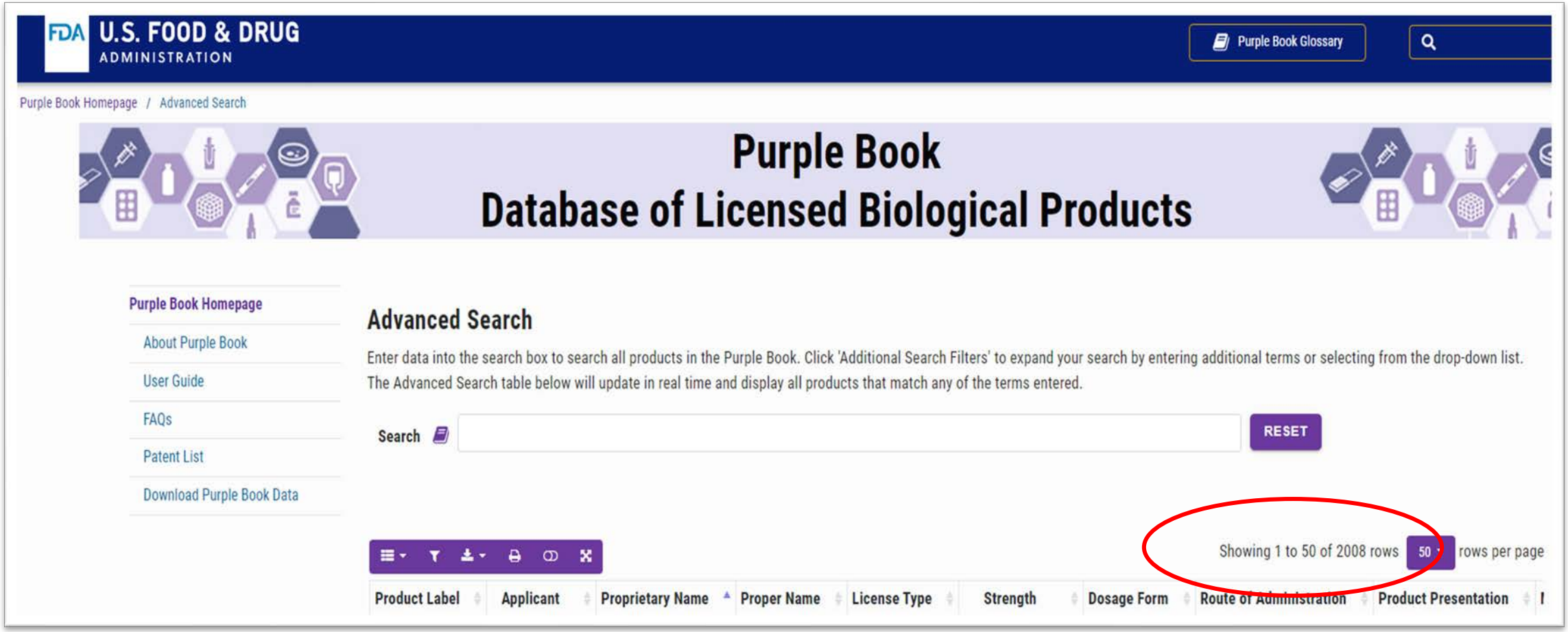


Australia
27m

USA
335m
12x larger




Source: https://purplebooksearch.fda.gov/advanced-search

# FDA Approved Cell and Gene Therapy Products

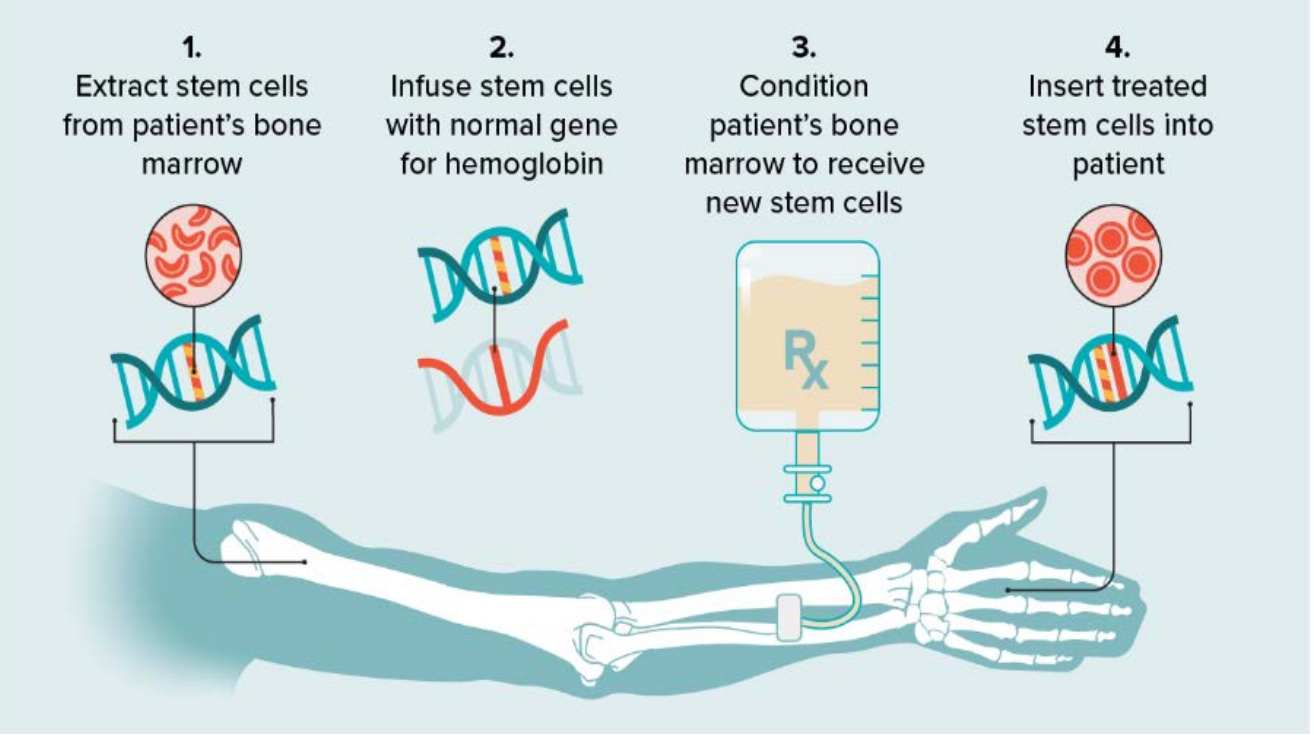
| Trade Name | Proper Name | Year Approved | Type | Indication |
|---|---|---|---|---|
| Provenge | sipuleucel-T | 2010 | APC, dendritici cells | Prostate cancer |
| Laviv | Azficel-T | 2011 | fibroblasts | Wrinkles |
| Gintuit | allogeneic Cultured Keratinocytes and Fibroblasts in Bovine Collagen | 2012 | Keratinocytes and Fibroblasts | Diabetic foot ulcers |
| Imlygic, Oncovex | talimogene laherparepvec | 2015 | oncolytic virus | Melanoma |
| MACI | autologous cultured chondrocytes on porcine collagen membrane | 2016 | Chondrocytes | Cartilage in knee |
| Kymriah | tisagenlecleucel | 2017 | T cell | Leukemia, Lymphoma |
| Yescarta | axicabtagene ciloleucel | 2017 | T cell | Lymphoma |
| Luxturna | voretigene neparvovec-rzyl | 2017 | Gene RPE65, via AAV2 | Biallelic RPE65 mutation-associated retinal dystrophy |
| Zolgensma | onasemnogene abeparvovec-xioi | 2019 | Gene SMN1 via AAV9 | Spinal muscular atrophy (SMA) |
| Tecartus | brexucabtagene autoleucel | 2020 | T cell | Leukemia |
| Breyanzi | lisocabtagene maraleucel | 2021 | T cell | Lymphoma |
| Abecma | idecabtagene vicleucel | 2021 | T cell | Myeloma |
| Rethymic | allogeneic processed thymus tissue–agdc | 2021 | thymus tissue | Congenital athymia |
| Stratagraft | Allogeneic cultured keratinocytes and dermal fibroblasts in murine collagen-dsat | 2021 | keratinocytes and dermal fibroblasts | Burn injuries |
| Carvykti | ciltacabtagene autoleucel | 2022 | T cell | Myeloma |
| Zynteglo | betibeglogene autotemcel | 2022 | Stem cell | Beta thalassemia |
| Skysona | elivaldogene autotemcel | 2022 | Stem cell | Cerebral adrenoleukodystrophy |
| Hemgenix | etranacogene dezaparvovec-drlb | 2022 | Gene F9, via AAV5 | Hemophilia B |
| Adstiladrin | nadofaragene firadenovec-vcng | 2022 | Gene IFNα2b, via ADV | Bladder cancer |
| Vyjuvek | beremagene geperpavec | 2023 | Gene COL7A1, via HSV-1 | Bullous epidermolysis |
| Elevidys | delandistrogene moxeparvovec-rokl | 2023 | Gene DMD, via AAVrh74 | Duchenne muscular dystrophy (DMD) |
| Roctavian | valoctocogene roxaparvovec-rvox | 2023 | Gene Factor VIII, via AAV5 | Hemophilia A |
| Lyfgenia | lovotibeglogene autotemcel [lovo-cel] | 2023 | Stem cell | Sickle cell |
| Casgevy | exagamglogene autotemcel [exa-cel] | 2023 | Stem cell | Beta thalassemia |
| Lantidra | donislecel | 2023 | islet beta cells | Type 1 diabetes |
| Omisirge | omidubicel-onlv | 2023 | stem cells | Infection post HCT |
| Lenmeldy | atidarsagene autotemcel | 2024 | Stem cell | Leukodystrophy (MLD) |
| Beqvez | fidanacogene elaparvovec-dzkt | 2024 | Gene, via AAVRh74var | Hemophilia B |
| Tecelra | afamitresgene autoleucel | 2024 | T cell | Sarcoma |
| Amtagvi | lifileucel | 2024 | T cell | Melanoma |

Source: PMID 35453231, PMID 33961738

# Recent International Approval – Cell-based Gene Therapy

First gene therapy for sickle cell Transfusion-Dependent ß-Thalassemia – CRISPR Gene editing

- EMA 15 Dec 2023, MHRA approved 15 Nov 2023
- FDA approved 8 Dec 2023 (SCD), 16 Jan 2024 (TDT)
- Saudi Food and Drug Authority (SFDA), 9 Jan 2024
- Autologous, edited using CRISPR targeting the BCL11A gene

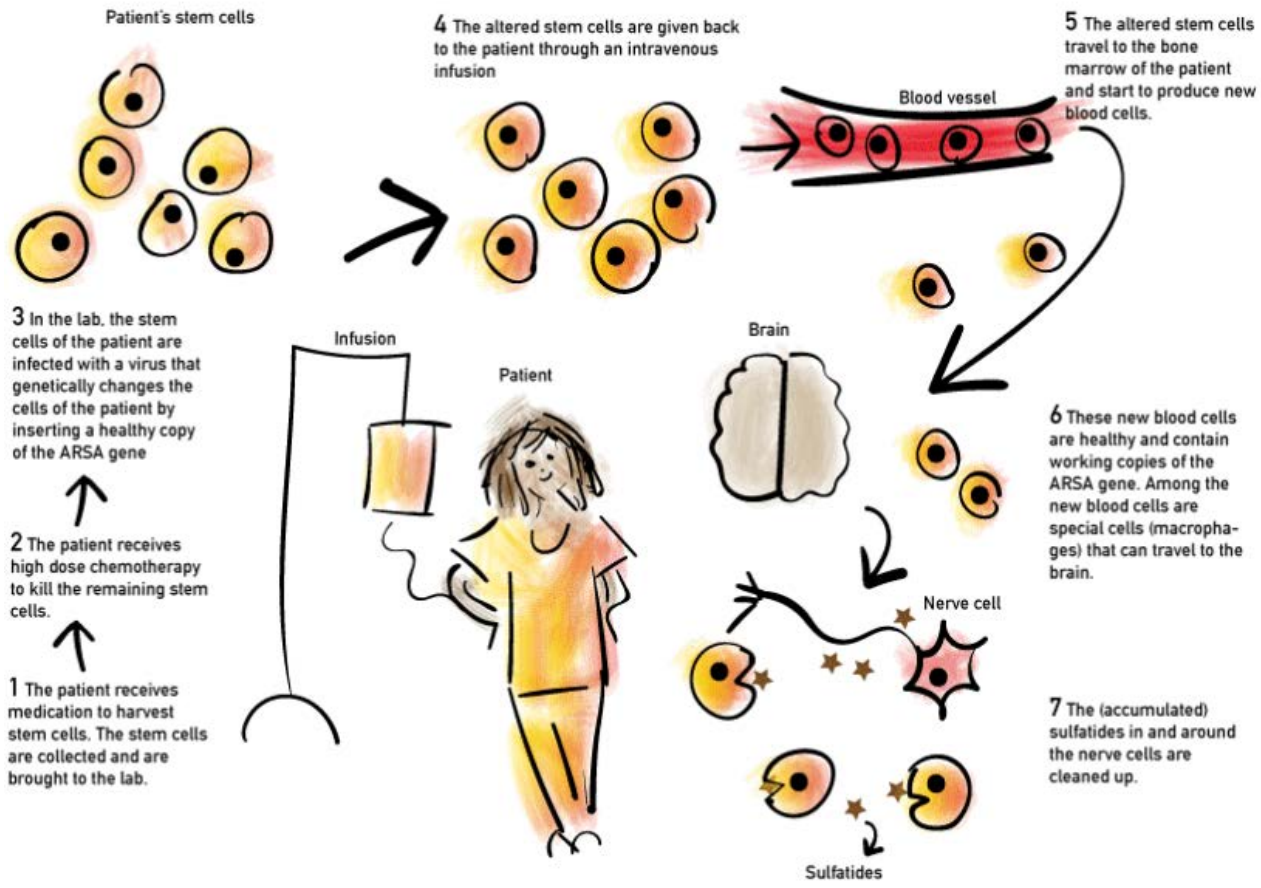



Source: https://www.healthline.com/health/sickle-cell-anemia-gene-therapy#procedure

# Recent International Approval – Cell-based Gene Therapy

First gene therapy for Metachromatic Leukodystrophy (MLD Pediatric)

- EMA 17 Dec 2020, Swissmedic 7 Dec 2023
- FDA 18 Mar 2024
- Autologous, CD34+ transduced with lentiviral vector encoding ARSA gene



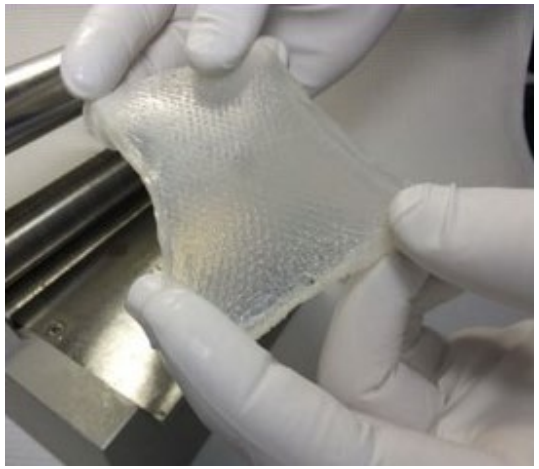

Schematic overview of hematopoietic stem cell therapy with gene therapy.

Source: https://www.mldinitiative.com/mld/treatments/

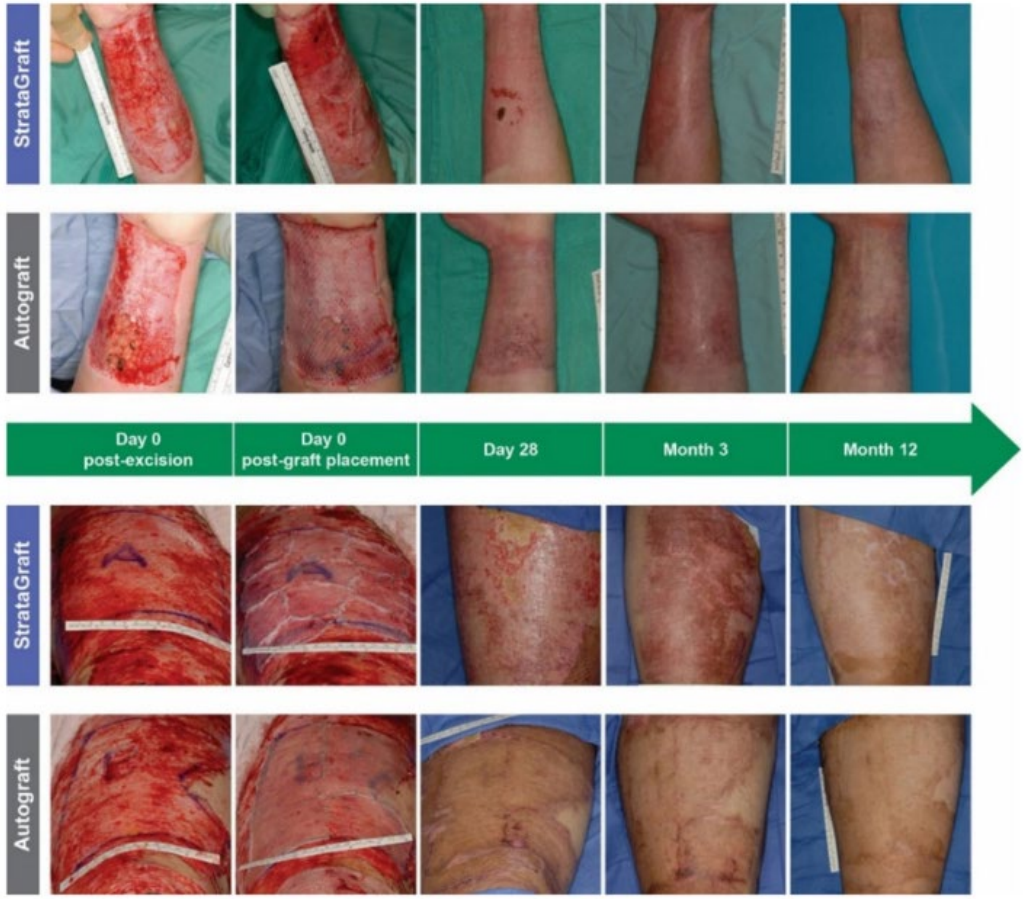
# Recent International Approvals – Tissue-based Therapy

Allogeneic cultured keratinocytes and dermal fibroblasts in murine collagen for deep burns, xenotransplant product

- FDA 15 June 2021
- Update 30 Jan 2024 – FDA no longer restricts these patients from donation of human products, e.g. organs, blood, plasma, milk, eggs, sperm.



Source: https://seed.nih.gov/portfolio/stories/Stratatech




-Images of StrataGraft tissue treatment sites and autograft treatment sites during the study from 2 representative subjects. The subject in the top photo array had a thermal burn of 8% TBSA and received refrigerated StrataGraft tissue and autograft on the forearms; the subject in the bottom photo array had a thermal burn of 28% TBSA and received cryopreserved StrataGraft tissue and autograft on the upper legs. TBSA, total body surface area.

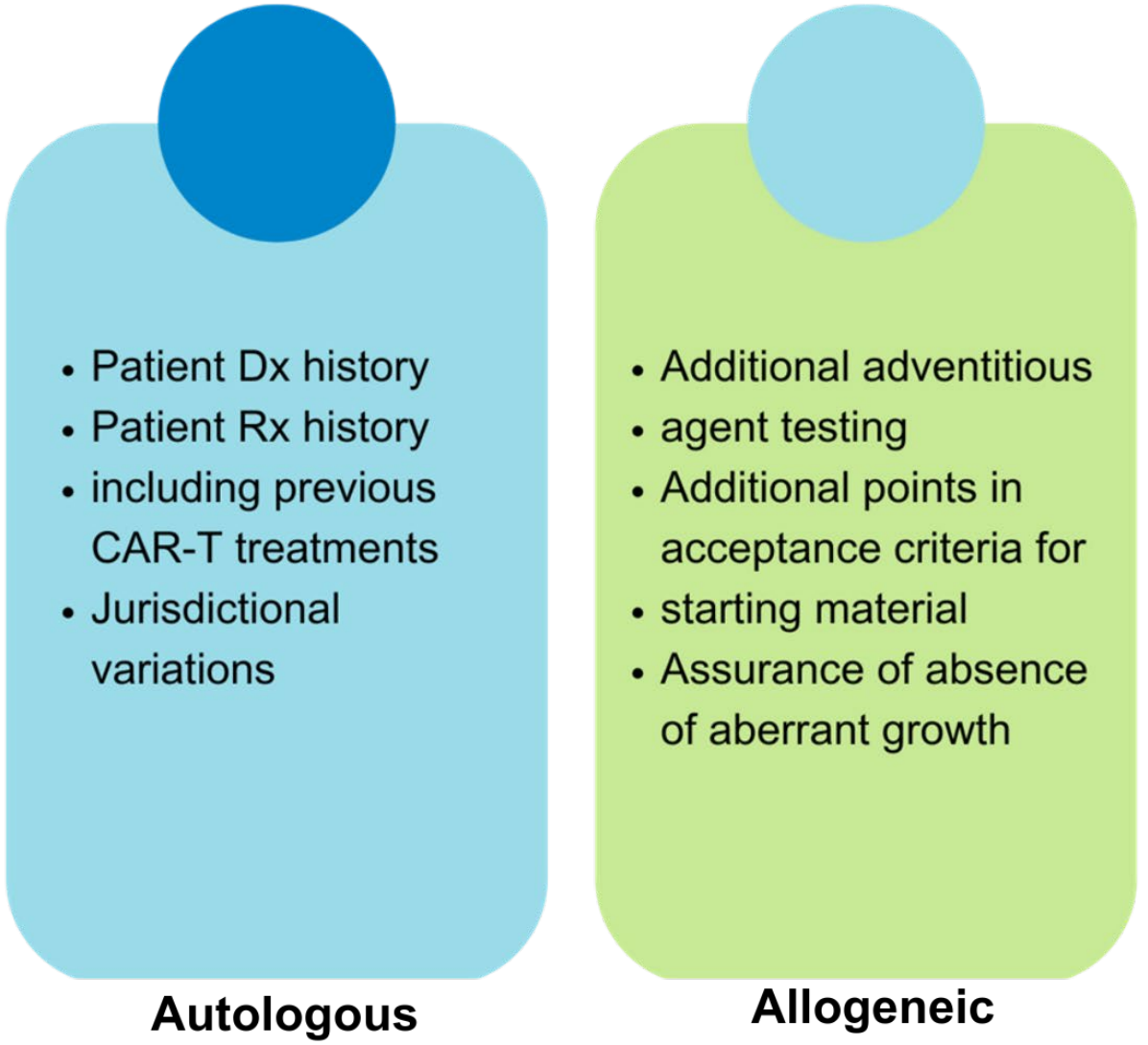
Source: DOI:10.1016/j.burns.2019.07.021

# Challenges with materials - starting cellular material

Products that use human cells as starting materials have inherent risks (e.g. transmission of disease) However, the risk varies with the product:

**For autologous (patient's own cells):** patient to patient variation impacts processing and final product quality.

**For allogeneic (donor cells):** additional donor screening is required to manage disease risk (each product lot treats multiple patients)



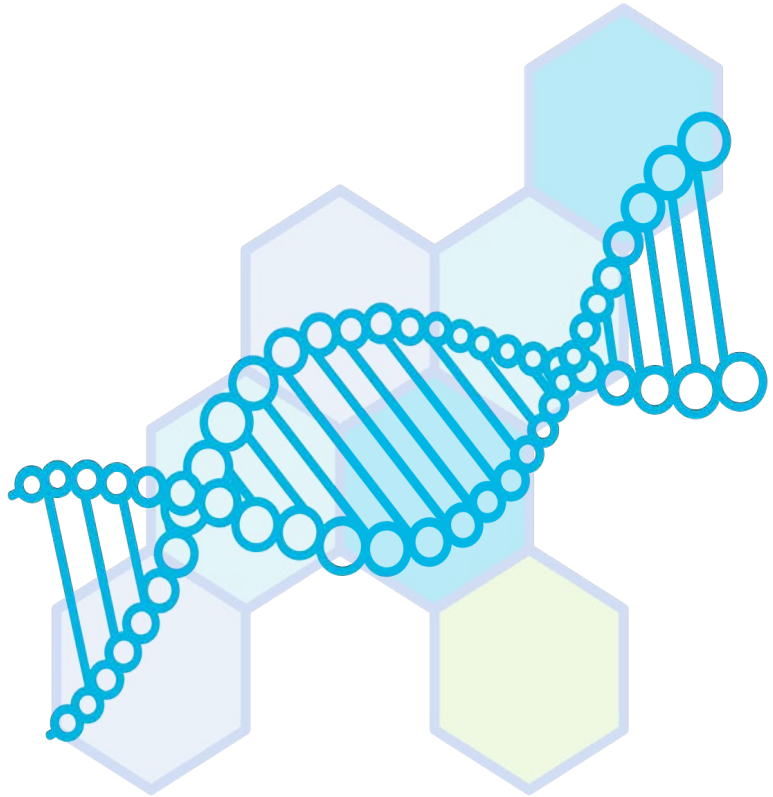
# Challenges with materials - Vector

Vectors are vehicles which deliver therapeutic genetic material. Vector is a starting material in cellular therapy, special considerations apply:

- When vector is used *ex vivo* to make a cell-based therapy the biologicals framework applies to the cell therapy product
- When vector is used *in vivo* as a gene therapy the medicines framework applies to the final product.

- Testing must consider:
  - Safety
  - Stability (support hold and storage times)
  - Biological activity (lot to lot)
  - Vector strength (lot to lot)

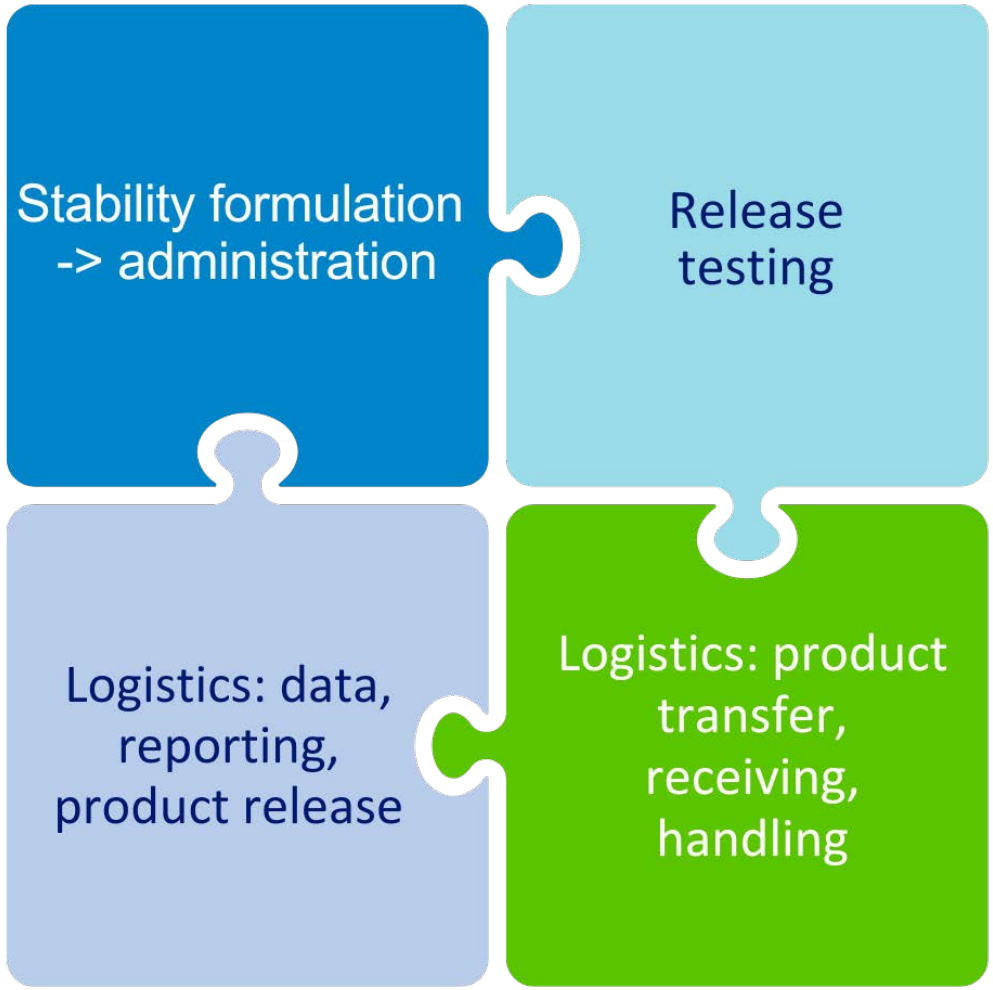
- Testing must cover MCB, WCB and virus banks as well as the vector itself.



# Logistics Challenge 1: Fresh Final Product

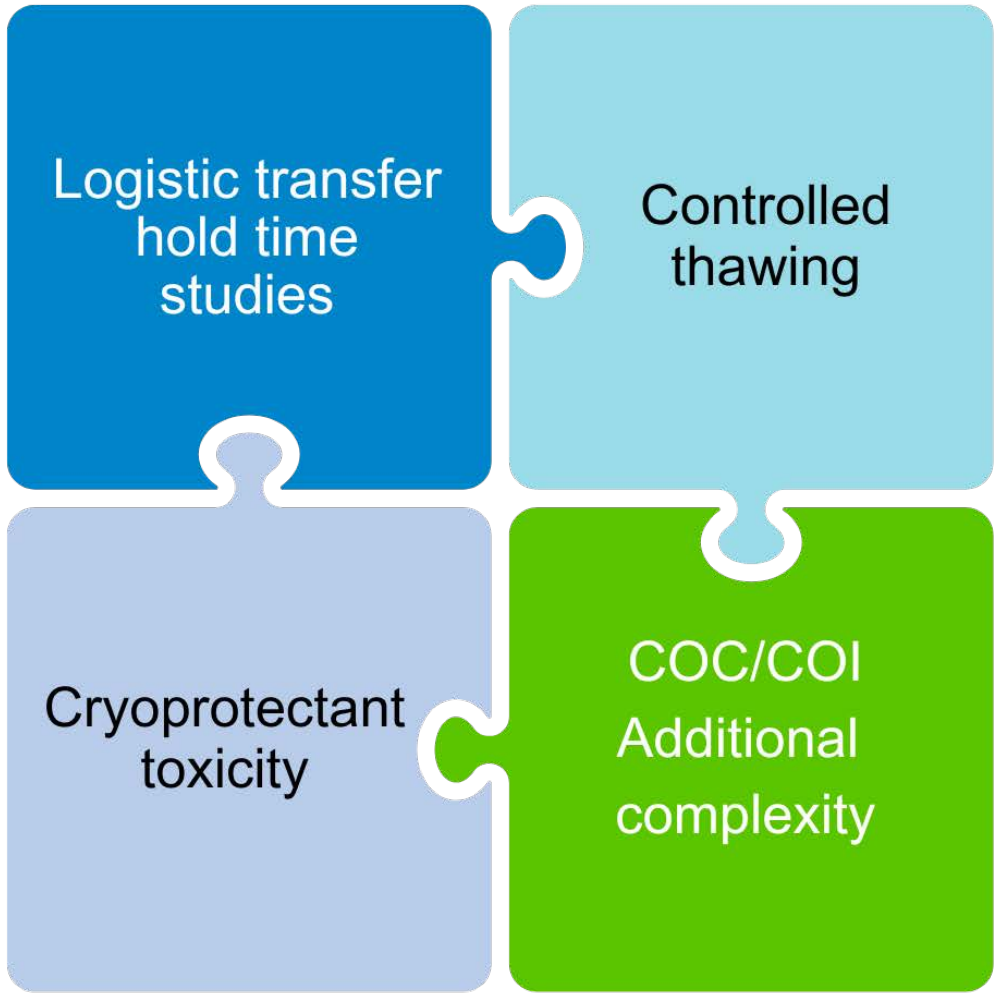
Manufactured cellular products may be released fresh (without cryopreservation) or frozen.

**Fresh product:** Timing restrictions on release and transfer

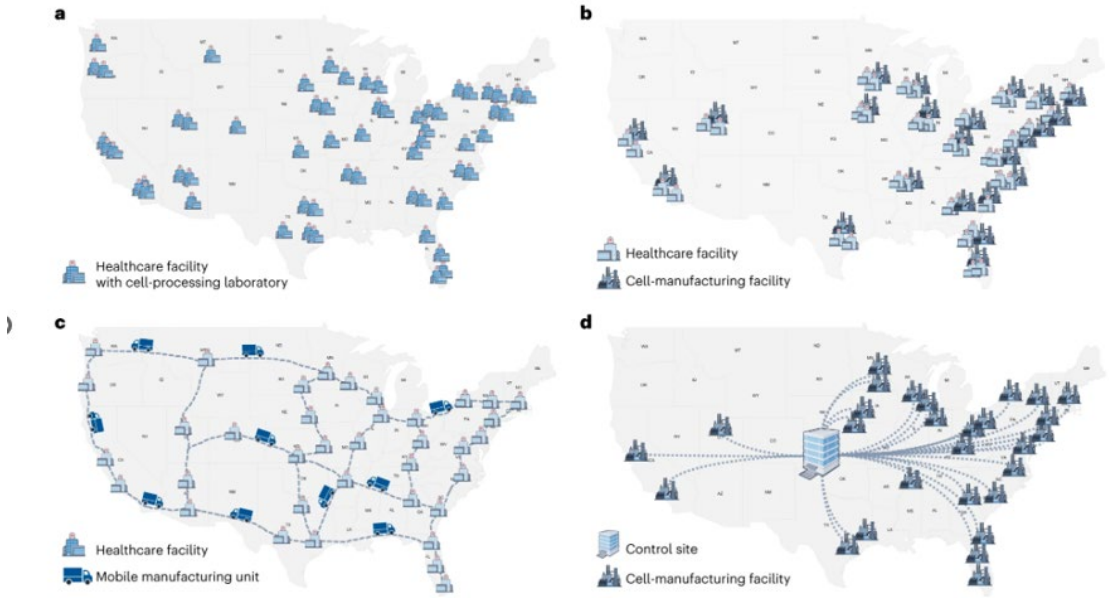


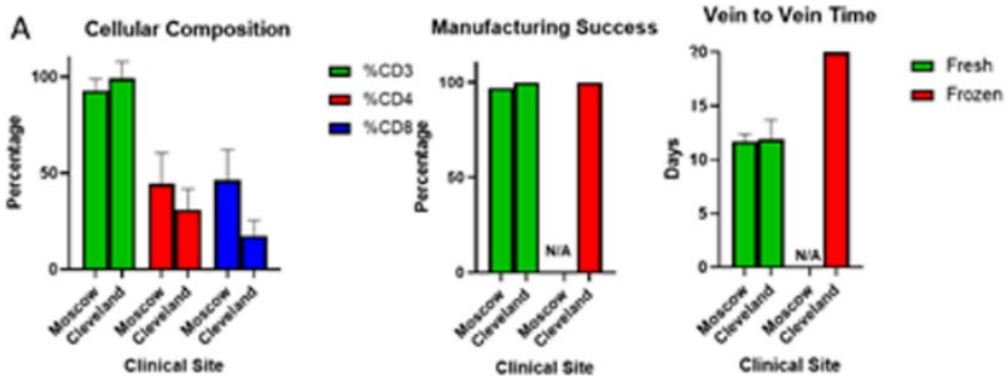
# Logistics Challenge 2: Frozen Final Product

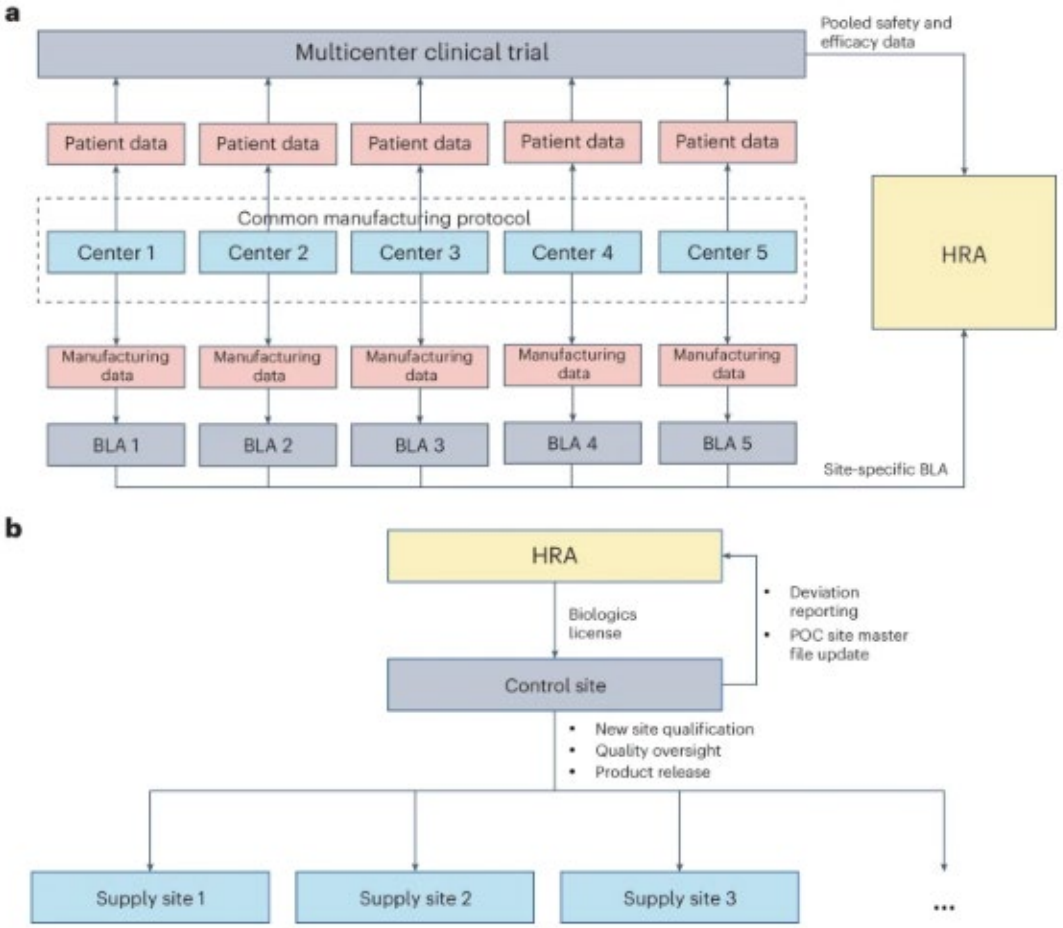
**Frozen product:** more flexibility in scheduling and logistics, but risks remain



# Logistics Potential Solution - Point of care manufacturing




Source: https://doi.org/10.1038/s41587-023-01981-8
https://doi.org/10.1038/s41467-021-27312-6

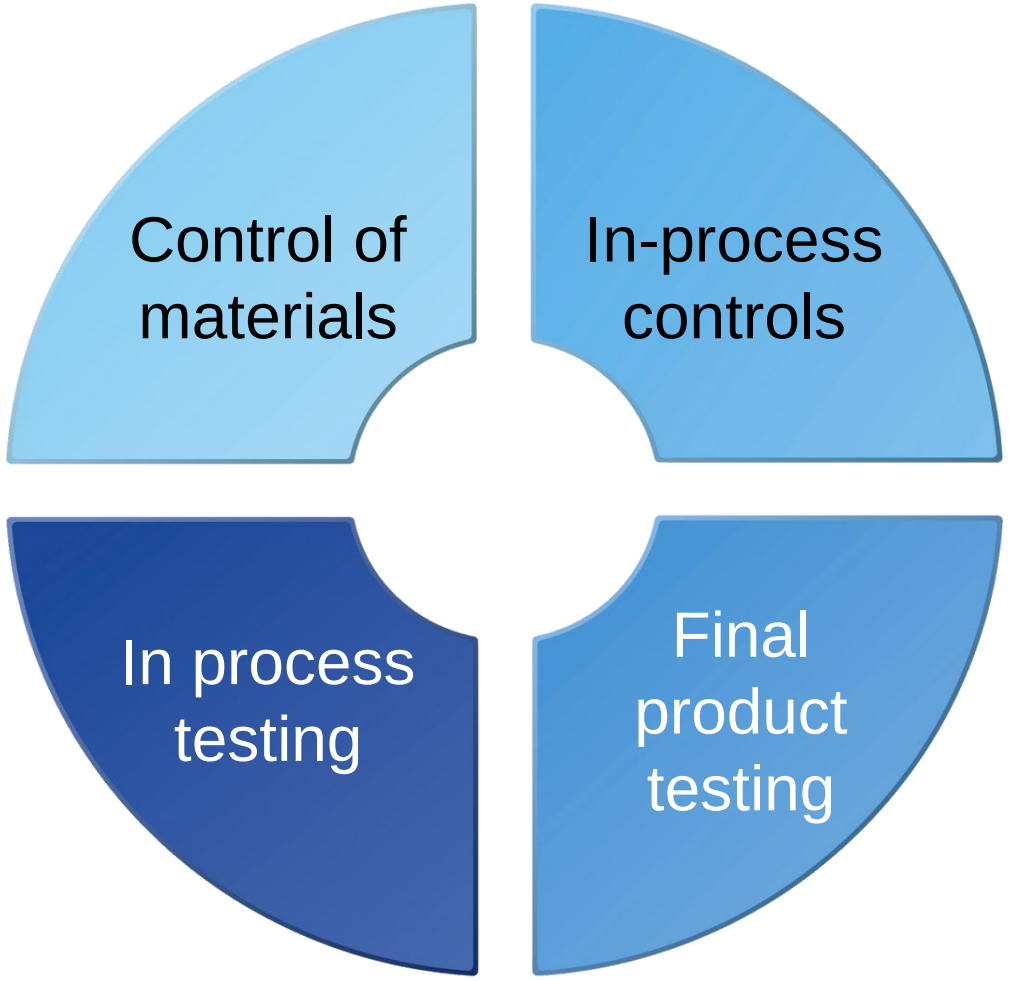
# Manufacturing Challenges

Manufacturing can be affected by unique factors:

1) Variability
- Donor-to-donor variability inherent to cellular starting material
- Multi-step complex manufacturing processes

2) Innovation in the field alongside product development lifecycle.
- Limited knowledge of product quality attributes
- Manufacturing changes throughout life cycle

Comparability assessments are likely to be required. Testing strategies become fundamental to supporting the evolution of the product.



# Knowledge Check

What is the most common Major deficiency from Biological inspections 2017-2024?

1. Premises and Equipment:
   Code Clauses 300 – 337

2. Quality Management:
   Code Clauses 100 – 117

3. Collection and Processing:
   Code Clauses 800 – 841

**Scan this QR code to particpate in this question**

# Common Major Deficiencies

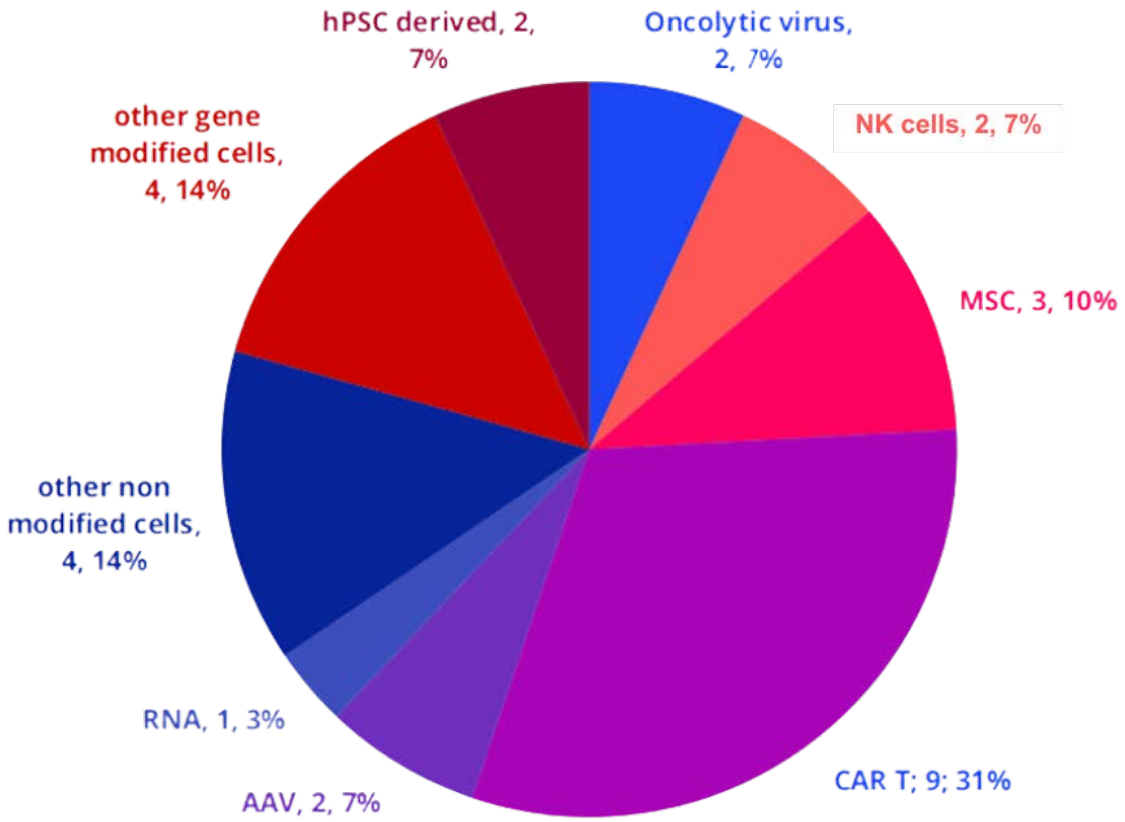
| Clause | Frequency | Topic | Example |
|---|---|---|---|
| 300 | 37% | Premises, facilities and equipment | • EM – risk assessments insufficient – no rationale for plate placement, number of personnel per space, organism inclusion (e.g. yeasts and moulds)<br>• Transfer of materials between zones<br>• Cleaning protocol/validation and removal of residues |
| 800 | 31% | Collection and processing | • Australian requirements for donor collection and labelling (TGO 108 and 107)<br>• Decontamination and transfer of materials<br>• Licence variations not submitted for process changes<br>• Aseptic technique training |
| 113 | 21% | Regular periodic quality reviews | |
| 115 | 15% | Quality system should be reviewed by management | |

# Common Other Deficiencies

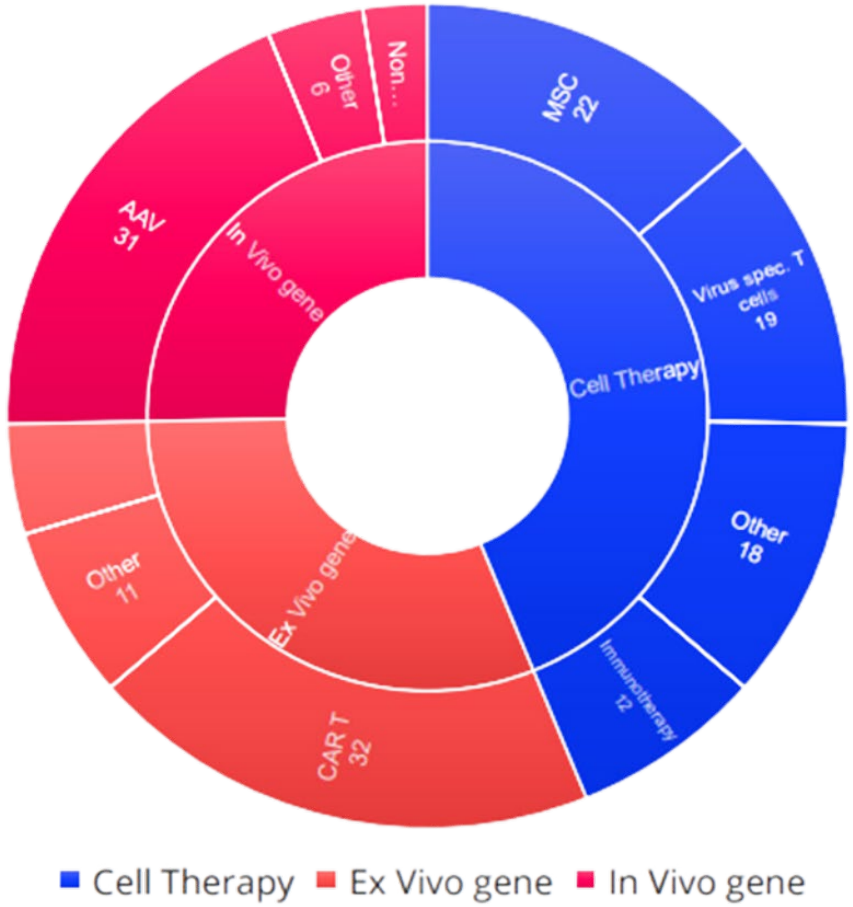
| Clause | Frequency | Topic | Example |
|---|---|---|---|
| 400 | 35% | Good documentation | • Records not completed<br>• Conflicting documentation<br>• Acknowledgement of new document versions<br>• Lack of procedures<br>• Incomplete procedures |
| 702 | 33% | Written procedure for product recall | • Out of hours contact and phone numbers<br>• Possibility for recall post infusion<br>• Not reflecting most current Biological recall process from TGA website<br>• capacity of being put into operation at any time |
| 116 | 27% | Change control system | |

# Australian Pipeline

Distribution of various advanced therapy modalities being developed by local companies in Australia




Distribution of trials by product type



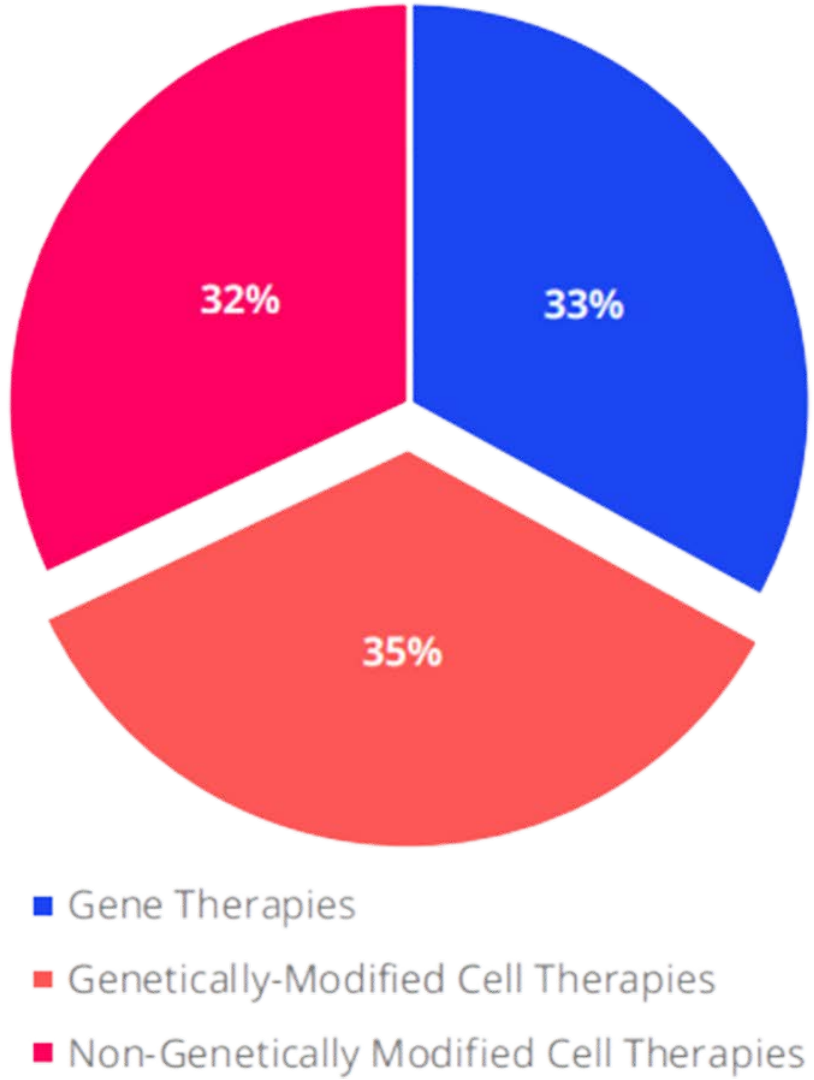
# Global pipeline

Globally from preclinical to preregistration phase 2848 products in cell and gene therapy space

100 products globally approved:

- 16 gene products
- 68 non-genetically modified cell products
- 16 genetically modified cell products

- Majority of products remain in preclinical development
- Similar distribution of approval by category type across geographic locations




Source: Pharmaprojects/ISCT 2024

# Export Pathway Update for Biological Products

## Key Developments

Biological products manufactured in Australia previously required identical listing in the ARTG for export.

Public consultation in Nov-Dec 2021 showed support for a dedicated export pathway for biologicals.

New framework allows for manufacturing and exporting of biological products not supplied domestically.

Medicines and Medical Devices had an 'Export Only' listing option, accommodating foreign specifications and labels.

Legislative change passed in March 2023 and commenced on June 21, 2023,
aligning biologicals with other therapeutic products.

Source: https://www.tga.gov.au/how-we-regulate/import-and-export/export/export-human-substances

# International frameworks and guidance in the ATMP space – updated guidance

Recently updated

- Update for guidance documents FDA (2024)
- PIC/S aide memoire
- Guidance flowcharts from EMA for ATMP – Quality, non-clinical and clinical
- MHRA - consultation for clinical trials

# Takeaways from the presentation today

1. ATMPs are regulated differently in different jurisdictions
2. In Australia, a Biological *comprises or contains human or animal cells, tissues or organs*.
3. Approvals and product development pipeline continues to grow both globally and domestically
4. Specific challenges exist for ATMPs across materials, logistics and manufacturing
5. The most common deficiencies seen during Biological inspections involve equipment and premises and collections and processing
6. Biological products can now be manufactured in Australia and exported via their own ‘Export Only’ pathway as legislation was passed in 2023
7. Engage early with the TGA: gmp@health.gov.au

# Questions?

**Scan this QR code with your device to submit a question**

GMP FORUM 2024

Australian Government

Department of Health and Aged Care

Therapeutic Goods Administration