Australian Government
Department of Health
Therapeutic Goods Administration

Dispelling GMP myths of human blood, blood components, tissues, cells and gene therapies

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Office of Manufacturing Quality
GMP Forum 2021

TGA Health Safety Regulation

Overview

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- Overview of regulation
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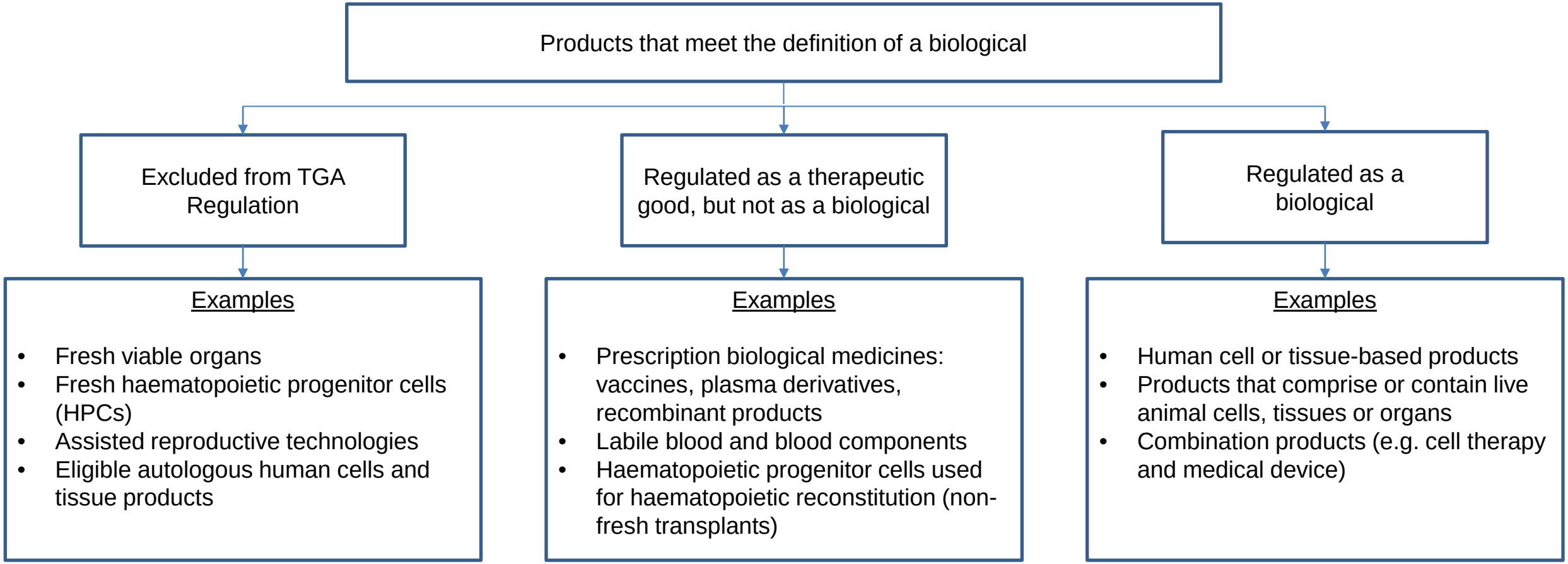
Relevant legislation, standards and guidance

There are a number of legislation, standards and guidance documents relevant to the regulation of blood and blood components, HPCs and biologicals.

Legislation	Standards	Guidance
• Therapeutic Goods Act 1989 (The ACT) • Therapeutic Goods Regulations 1990 (The Regulations) • Legislative instruments, including ➢ Therapeutic Goods (Charges) Regulations 1990 ➢ Therapeutic Goods (Things that are not biologicals) Determination No. 1 of 2011 ➢ Therapeutic Goods (Things that are Biologicals) Specification 2019 ➢ Therapeutic Goods (Manufacturing Principles) Determination 2018 ➢ Therapeutic Goods (Excluded Goods) Determination 2018	• Infectious disease minimization Standard (TGO 88) - Standards for donor selection, testing, and minimising infectious disease transmission via therapeutic goods that are human blood and blood components, human tissues and human cellular therapy products • Labelling standard (TGO 87) • Product specific standards (TGOs) ➢ human musculoskeletal tissue (TGO 83) ➢ human cardiovascular tissue (TGO 84) ➢ human ocular tissue (TGO 85) ➢ human skin (TGO 86) ➢ faecal microbiota transplant (FMT) products (TGO 105) • Default standards ➢ British Pharmacopoeia ➢ United States Pharmacopeia – National Formulary ➢ European Pharmacopoeia	• Australian Regulatory Guidelines for Biologicals • Manufacturing biologicals

Overview of regulation

How therapeutic goods comprised of or contained blood, blood components, tissues, cells and gene therapies are regulated?.



Regulation- Blood and blood components

- Blood means whole blood collected from a single human donor and processed either for transfusion or further manufacturing*.
- Blood components means the therapeutic components of blood that can be prepared by centrifugation, filtration and freezing, but not including haematopoietic progenitor cells (HPCs)*.

For example: red blood cells, white blood cells, platelets, plasma, serum, platelet-rich plasma [PRP], platelet-rich fibrin [PRF], conditioned serum

*As defined in TGO 88

How these products are regulated?

- Exempt from TGA regulation
- Regulated as therapeutic good but not a biological
  - the Therapeutic Goods Act 1989 – Therapeutic Good (Manufacturing Principles) Determination No 1
  - Obtain GMP licence under Part 3-3 of the Act
    - Australian Code of GMP 2013
  - Technical Master File (TMF) lodged by manufacturer
    - Demonstrate compliance with TG0 88, TGO 87 and TGO 102 Standard for Blood and Blood Components
- Regulated as medicines – obtain a GMP licence and registered in the ARTG
  - Products derived through plasma fractionation

Regulation - Haematopoietic progenitor cells (HPCs)

- Haematopoietic progenitor cells means primitive multipotent cells capable of self-renewal as well as differentiation and maturation into all haematopoietic lineages*. For example, HPCs manufactured from cord blood

How HPCs are regulated?

- Cord blood HPCs are regulated as therapeutic goods but not a biological
  - ❖ under the Therapeutic Goods Act 1989 – Therapeutic Good (Manufacturing Principles) Determination No 1 (not excluded good)
  - ❖ Obtain a GMP Licence under Part 3-3 of the Act – Comply with the cGMP (2013) requirements
  - ❖ Submit a TMF that complies with the product specific standard requirements- TGO 94 Standard for Haematopoietic Progenitor Cells derived from Cord Blood, TG88, TGO 87.
- For non-cord blood HPCs, or materials used in the manufacture of cord and non-cord blood HPCs, there is no product specific standard, thus the BP, Ph. Eur. and the USP default standards are applicable.

*As defined in TGO 88

Regulation - Haematopoietic Progenitor cells (HPCs)

Depending on the specific activities undertaken by a manufacturer, relevant monographs from the default standards may include, but are not limited to:

- *Human Haematopoietic Stem Cells* (Ph. Eur. monograph 2323)
- Appendix XIV C. *Test for Bacterial Endotoxins* (LAL Test) (Ph. Eur. method 2.6.14)
- SC I C. *Bacterial Endotoxin Testing*
- Appendix XVI A. *Test for sterility* (Ph. Eur. method 2.6.1)
- Appendix XVI E. *Microbiological control of cellular products* (Ph. Eur. method 2.6.27)
- *Dimethyl sulfoxide* (Ph Eur monograph 0763)
- Appendix XIV N. *Numeration of CD34/CD45+ cells in haematopoietic products* (Ph. Eur. method 2.7.23)
- *Dextran 40 for injection* (Ph. Eur. monograph 0999)
- *Dextran 40 for intravenous infusion* (BP 2009 volume III)
- Appendix XIV N 2. *Colony-forming cell assay for human haematopoietic progenitor cells* (Ph. Eur. method 2.7.28)

Regulation- Autologous human cell and tissue products (HCT)

- What are autologous HCT products?
  - HCT products are those that comprise, contain or are derived from human cells and tissues that are removed from, and applied to, the **same person**, i.e. the donor and the recipient are the same. Those products are commonly referred to as 'stem cell products'.

- Examples of autologous HCT products
  - blood and blood components (red cells, plasma, serum, platelets, platelet-rich plasma [PRP], platelet-rich fibrin [PRF], and conditioned serum)
  - skin grafts for treatment of burns
  - bone grafts
  - genetically-altered lymphocytes to target cancers
  - adipose-derived cell extracts (including stromal vascular fraction (SVF))

Regulation- Autologous human cells and tissues products

- The level of regulation for autologous HCT products is based on the level of risk(s) associated with their use They are:
  - excluded from TGA regulation
    - e.g. goods that are fresh viable human organs or parts of human organs
  - regulated by TGA with exemptions from some requirements, e.g. fresh blood and blood components and HPCs.
  - fully regulated by TGA (as a medicine or biological), e.g. CAR- T Cells

Regulation- Autologous human cells and tissues products

- Exempted autologous cell and tissue products must meet the following criteria*:
  - Not advertised directly to consumers
  - Comply with all applicable standards
  - Report adverse events to the TGA
  - Conduct recalls
  - Maintain evidence to demonstrate safety and efficacy of the product

*The Australian Regulatory Guidelines for Biologicals (ARGB) - *Exempt autologous human cells and tissues*

Regulation: Biologicals

- The GMP requirements of these products are set out in The Act and The Regulations, and described in the Australian Regulatory Guidelines for Biologicals (ARGB).
- It is the Sponsor's responsibility to ensure that GMP licences are obtained for all of the involved manufacturers of the a biological. This applies to all:
  - Donors infectious disease testing facilities
  - Microbiology testing facilities
  - Physicochemical testing facilities
  - Sterilisation and/or irradiation facilities
  - Packaging facilities.

- Generally, all testing facilities perform testing that impact the acceptance for release or rejection of a biological.
- The Sponsor is required to submit evidence that all manufacturers are GMP licenced/certified by TGA or the licencing/certification process has been initiated. GMP accreditation must be approved prior to any decision made to include the product in the ARTG.

Good Manufacturing Practice (GMP) – Why?

- In Australia, the *Therapeutic Goods Act 1989* requires, with certain exceptions, that manufacturers of therapeutic goods hold a licence. It is an offence, carrying heavy penalties, to manufacture therapeutic goods for human use without a licence unless the manufacturer or goods are exempt from this requirement.

- The term GMP is used internationally to describe a set of principles and procedures which, when followed by manufacturers of medicines and biologicals, helps ensure that the products manufactured will have the required quality.

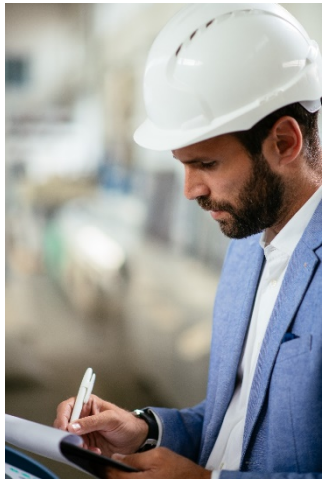
- Adherence to the **GMP** regulations assures the identity, strength, quality, and purity **of** medicines and biologicals by requiring that manufacturers adequately control manufacturing operation.

- Manufacturers of therapeutic goods are regularly inspected by the TGA using a risk-based approach to ensure compliance with GMP standards**

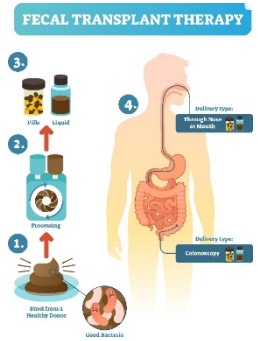
***The Australian Code of GMP for human blood, blood components, human tissues and human cellular therapy products (2013) and Therapeutic Goods Orders (TGOs) and if no TGOs, BP/EP/USP*

Equipment

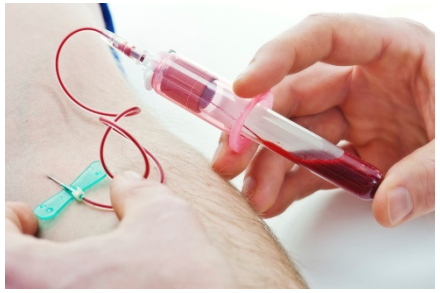
Building and Facility



Inspector



Manufacture - Processing



Collection of blood

Documentation

Released Product

Labelling and Packaging

Quality Control

Computers

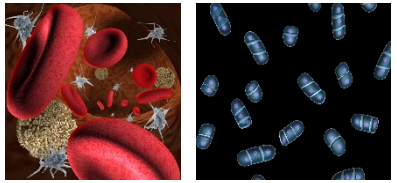
Critical Materials and storage

Quality Options

Right product, meeting specified attributes

Right strength & or concentration

Right expiry date



Batch record (single and multiple batches)

Right volume, weight and appearance

No contamination and or no mix-up

What are the benefits of GMPs?

- They outline a Quality System that reduces or prevents errors
- Ensures that products are safe for use in human
- Prevent/control contamination and cross-contamination
- Minimises variation in quality and / or potency of the final product
- Ensure reproducible physiological activity
- Prevent side effects and toxicity due to variations in the final biologicals products ~~and their potency~~
- Prevent mislabelling to ensure traceability

cGMP: The Basics

- **Quality Control (QC)**
  - Product meets specifications and QC testing, safety, and effectiveness must be designed and built into the product
  - Quality cannot be inspected or tested into a final product
- **Quality Assurance**
  - Systems ensure control and consistency
  - Validation, validation, validation
- **Documentation**
  - If it is not documented, it did not happen

cGMP: Starting Materials and Critical Materials

- Starting materials- cells, tissues, blood and blood components
- Excipients
- Other critical materials that have contact with the product
- Audit critical suppliers on regular basis and according to requirements
  - Before entering into contract, review regulatory history
  - Monitor regulatory compliance

cGMP: Critical Materials

- Inspection and testing of incoming critical material
- Identification and segregation of quarantined, released and rejected materials

cGMP: Buildings and Facilities

- Separate or defined areas as are necessary to prevent contamination or mixups
- Air filtration systems (HVAC) in production areas
- Sanitation
- Temperature and pressure monitoring, as required

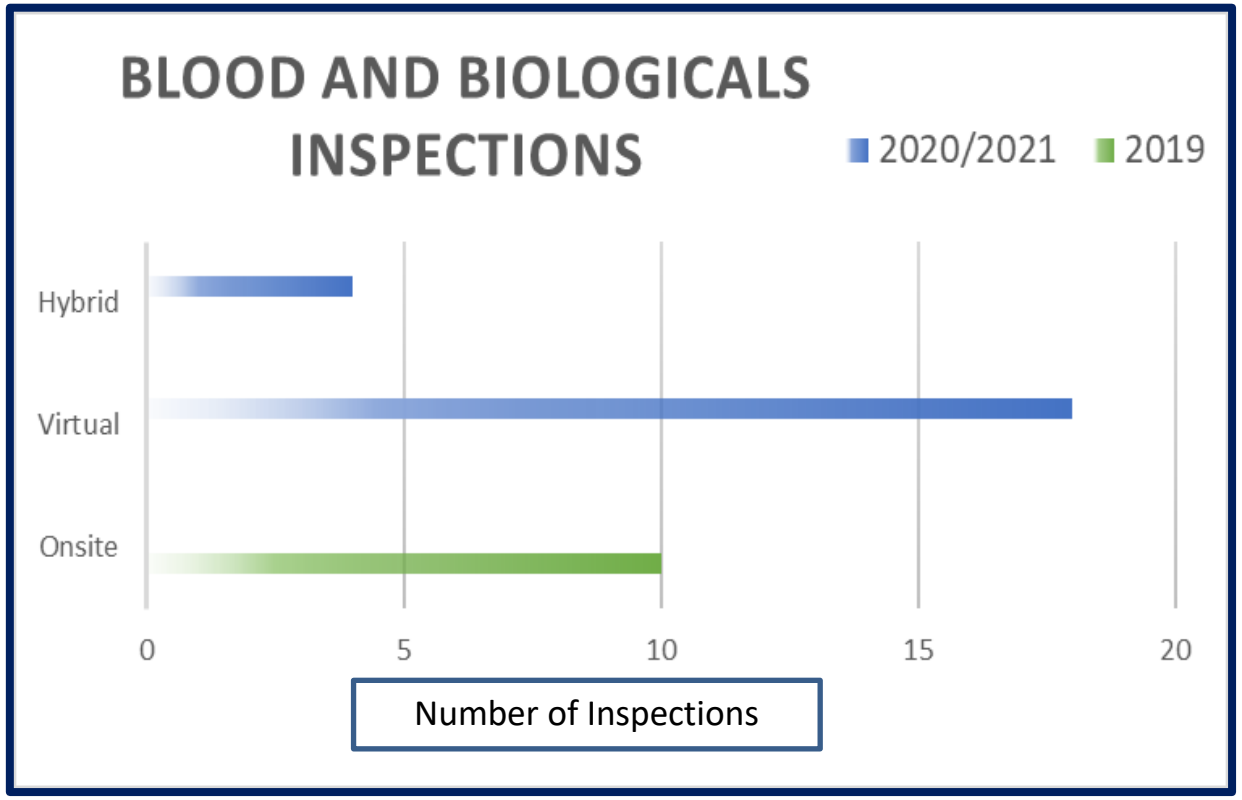
cGMP: Production and Process Controls (SOPS)

- Written production and process control procedures shall be followed in manufacturing and all relevant activities must be documented at the time of performance.
- If validation is required according to risk base – validate and or verify
- Any deviation from these procedures must be recorded and explained and or justified.

Computerised System

- The validation procedure for implementing the computerised system.
- The change control for the computerised system.
- Configuration management of the computerised system
- Training to use the computerised system

Data on inspection 2019 (Onsite) – 2020 - 2021(Remote and Hybrid)



Commonly observed issues - Onsite

- Meeting conditions of registration
- Personnel awareness of the principles of GMP and ongoing competency training
- Facility requirements – specification for the environment and lack of environmental monitoring
- Deviations / non-conformances are not fully recorded, investigated with the objective of determining the root cause, no appropriate corrective and preventive action implemented and if implemented no review of effectiveness;
- Annual Product Review not managed according to the Code requirement (no review of adequacy of any other previous APRs
- Change and risk management
- Personnel not carrying the process as required by the procedures
- Management of critical material specifically entry into Biological Safety Cabinet (BSC)
- Ongoing reviews of key validations
- Aseptic processing and media fills
- Transport validations

Commonly observed issues – Virtual & Hybrid

- Meeting conditions of registration
- If you make claim you need to meet the basis of the claim- for example the clean room grade
- Inadequate investigations of non-conformances
- Validations of all the manufacturing processes- including validation of changes, e.g.
  - tissue and finished products transportations
  - Product Microbial Contamination Testing
  - Quality Control testing (In process and release for supply)
- Aseptic technique validation
- Training
- All processes and associated activities in the manufacture of product were not documented or not well documented
- Records not maintained to demonstrate that the quality system had operated effectively and due to the review of more records – increased sighting of alteration of records
- Management of critical material – quarantine vs released and approved specifications
- Vendor qualification

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