



Australian Government
Department of Health
Therapeutic Goods Administration

Biovigilance

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TGA Health Safety
Regulation

Outline

- What are biologicals?
- Regulatory framework for biologicals
- What is biovigilance?
- Responsibilities of sponsors of biologicals
 - reporting adverse events
 - recalls
- Sponsors' biovigilance systems
- TGA process
 - development of draft guidance, consultation, finalisation of guidance
 - regulatory aspects
- Questions and discussion

What are biologicals?

Short
definition
=
human
tissue and
cell-derived
products

Definition of a biological in the TG Act (Part 3-2A–Biologicals)

32A Meaning of *biological*

(1) Subject to subsection (3), a biological is a thing that:

(a) either:

- (i) comprises, contains or is derived from human cells or human tissues; or
- (ii) is specified under subsection (2); and

(b) is represented in any way to be, or is, whether because of the way in which it is presented or for any other reason, likely to be taken to be:

- (i) for use in the treatment or prevention of a disease, ailment, defect or injury affecting persons; or
- or
- (ii) for use in making a medical diagnosis of the condition of a person; or
- (iii) for use in influencing, inhibiting or modifying a physiological process in persons; or
- (iv) for use in testing the susceptibility of persons to a disease or ailment; or
- (v) for use in the replacement or modification of parts of the anatomy in persons.

[In addition, the Secretary can specify things to be or not to be biologicals by instrument]

Regulatory framework for biologicals

- Provides the legislative basis for the regulation of human tissue and cell-derived products that are supplied in, or exported from, Australia.
- Legislation commenced May 2011 – transition period (3 years+)
- Information on TGA website at <https://www.tga.gov.au/regulatory-framework-biologicals>
- Australian Regulatory Guidelines for Biologicals at <https://www.tga.gov.au/publication/australian-regulatory-guidelines-biologicals-argb>
- Not biological medicines
- Similar, but not identical, to the EMA's Advanced Therapy Medicinal Products (ATMPs) which are medicines for human use that are based on genes or cells

What is biovigilance?

- *The science and activities relating to the detection, assessment, understanding and prevention of adverse events or any other problems related to biologicals*
- Therapeutic product vigilance in Australia
 - Pharmacovigilance
 - Medical devices vigilance
 - Biovigilance
- Includes quality issues
- Other terms - post-market monitoring / surveillance
- Systematic collection and analysis of information to improve patient safety

Responsibilities of sponsors of biologicals

- *Therapeutic Goods Act 1989* and *Therapeutic Goods Regulations 1990*
- Sponsors of biological products on the Australian Register of Therapeutic Goods (ARTG) must report to the TGA
 - **Serious threat to public health = 48 hours**
 - **Serious adverse event = 10 calendar days**
 - **Near serious adverse event = 30 calendar days**
- This terminology used as biologicals legislation was based on devices legislation
- All classes of biologicals
- Uniform Recall Procedure for Therapeutic Goods
 - **Recalls, quality defects, contaminated biologicals = as soon as possible**

Biovigilance guidance

- Draft guidance has been developed based on the TGA pharmacovigilance and medical device vigilance guidance
- Also based on relevant pharmacovigilance guidance, standards and terminology
 - European Medicine Agency (EMA) Good Pharmacovigilance Practice (GVP)
 - International Conference on Harmonisation of Technical Requirements Technical Requirements for Pharmaceuticals for Human Use (ICH)

Adverse events (1)

- **Any undesirable medical event that occurs in temporal relationship with (during or after) the use of a biological product**
 - symptom, sign (e.g. abnormal laboratory finding), disease or injury
 - at least a reasonable possibility of a causal relationship between the use of the biological and the event
- **Serious adverse event**
 - an event or occurrence that led to a death or serious deterioration in the state of health of a patient, a user of the biological or another person
- **Near serious adverse event**
 - an event or occurrence that, if it occurred again, might lead to the death or serious deterioration in the state of health of a patient, a user of the biological or another person

Adverse events (2)

- AEs may relate to the biological itself or any aspect of the biological
 - Solutions
 - Excipients
 - other substances or materials
 - Packaging
 - delivery systems

Adverse events (3)

- Potential for AEs depends on
 - origin of the biological (autologous or allogeneic)
 - ability of cells constituting a biological to proliferate or differentiate
 - ability of the biological to initiate an immune response
 - life span of the biological *in vivo*
 - site and mode of administration
 - type and level of cell manipulation during production
 - storage time and conditions
 - out-of-specification findings identified during in-process testing of the biological

Serious adverse events (SAEs)

- An adverse event for which one or more of the following is true
 - results in death
 - is life-threatening
 - requires inpatient hospitalisation
 - prolongs existing hospitalisation
 - results in persistent or significant disability or incapacity, including permanent impairment of a body function or permanent damage to a body structure
 - necessitates medical or surgical intervention to prevent permanent impairment of a body function or permanent damage to a body structure
 - is a congenital anomaly or birth defect
 - is a medically important event

How to report adverse events

- Minimum data for a valid report
 - an identifiable patient (but do not send name to the TGA)
 - one or more suspected biological or delivery system or other aspect of a biological
 - one or more suspected adverse events (events with a reasonable possibility of causal relationship)
 - one or more identifiable reporters
- Only adverse events that have occurred in Australia
- Provide as much information as possible to facilitate assessment of the AE
- Range of reporting formats available, including direct data entry online
 - More information on TGA website at <https://www.tga.gov.au/reporting-problems>
 - Will develop specific formats for biologicals – currently use either medicines or medical devices reporting processes

Examples

- Some reports of tissue related adverse events received over the past 3 years
 - Pulmonary heart valve – leaflet tear and bleeding
 - Heart valve – sterility concerns – recipient had an infection
 - Bone (femoral head) – several reports relating to new information about the donor such as malignancy

Serious threat to public health

- Any identified safety issue which may change the benefit-risk assessment of the product and require action to eliminate or reduce that risk, such as
 - a report of an unexpected or previously unknown serious or near serious adverse event
 - a change in the nature, severity or frequency of expected (known) adverse events
 - the identification of previously unknown risk factors
 - the transmission of an infectious agent, including reactivation of any viral vector
 - a signal of a possible teratogenic effect
 - a signal of possible tumorigenicity
 - unexpected lack of efficacy
 - issues related to the raw materials used in the biological
 - issues related to the delivery system used for the biological
 - issues due to misinformation in the product documentation
 - issues related to use outside the approved indication or intended use

How to report a serious threat to public health

- In writing and sent by email to the Signal Investigation Coordinator (si.coordinator@tga.gov.au)
 - Subject line = ‘Urgent – serious threat to public health – [descriptor: name or number of biological, name of sponsor, or some other descriptor]’
 - describe the evidence for the threat
 - indicate the action that the sponsor is proposing to take to eliminate or reduce the risk
 - the action may relate to conditions of inclusion in the ARTG including amendments to the label or the product information or any other change
 - clearly identify the person in Australia who is taking responsibility on behalf of the sponsor for the accuracy and veracity of the information in the report
 - include contact details of the person reporting on behalf of the sponsor, preferably the nominated biovigilance contact person

Recalls and quality issues

- Notify suspected or confirmed quality defects and contaminated or counterfeit biological products to the TGA with the least possible delay
 - *Uniform Recall Procedure for Therapeutic Goods (URPTG)*
 - New version will include biologicals
- May be necessary to implement urgent measures to protect public health
 - for tissues usually “Hazard Alerts” but may involve a recall
- Use the *Human blood and tissues recall report form* or phone TGA Recalls on 1800 020 512
 - see *Contact details for enquiries about product recalls* on the TGA website at <https://www.tga.gov.au/product-recalls#contacts>

System for Australian Recall Actions (SARA) - Biologicals

Recall action commencement date	Product name / description	Reason for recall action	Recall action
17/06/2014	Pulmonary Valve Allograft	Staph epidermis isolated from nutrient broth	Hazard Alert
24/04/2014	Corneo-scleral Disc (Normothermic)	Potentially untraceable microbiology results	Hazard Alert
31/05/2013	Bone Fragments - Milled irradiated femoral head	At 2 nd donation, donor found to have mantle cell lymphoma	Hazard Alert
17/04/2013	Pulmonary Valve Transplant	Positive microbiological culture from implant tissue culture	Hazard Alert
19/03/2013	RegenerOss Allograft Block Max/Mand Blocks	Assays used to test donors for HBsAG and Hep C not licensed for donor testing	Hazard Alert
1/03/2013	Bone Fragments - Milled irradiated femoral head	Donor melanoma removed 10 months after donation	Hazard Alert
15/02/2013	Bone Unprocessed - Whole femoral head non-irradiated allograft	Donor diagnosed with oesophageal cancer	Hazard Alert
22/01/2013	Corneal Grafts	Multiple myeloma found later in bones from same donor	Hazard Alert
8/01/2013	QHVB Pulmonary Allograft Conduit (Human cardiovascular tissue)	Retained samples showed positive microbial growth	Hazard Alert

Biovigilance system

- Not a legislated requirement
 - but
- Needed to enable sponsors to meet their biovigilance responsibilities including
 - routine biovigilance
 - additional biovigilance specified in the Risk Management Plan (RMP)
 - where an RMP is required
 - all traceability and any other requirements specified as conditions of registration
 - the critical analysis of adverse events and other safety and quality information
 - any activities needed to mitigate an identified safety issue

Traceability

- Sponsor needs to be able to locate and identify a biological during any step in the process from donor to recipient (including disposal)
- The donor, tissue establishments, manufacturing facilities, medical facilities and recipients must all be identifiable
- Traceability also covers the ability to locate and identify all relevant data relating to products, materials and people that have come into contact with the biological
- Required
 - Therapeutic Goods Order No. 87 6(1)
 - Class 3 and 4 biologicals (where an RMP is required) - a product specific condition of registration requires traceability to the recipient

Where to from here?

- Biovigilance guidance – drafting now completed
- The draft guidance was endorsed by the TGA Regulatory Practice Committee (RPC) for consultation
- Consultation will commence shortly and be in parallel with RMP guidance which has been revised to include specific biologicals advice
- Will be a public consultation – information on TGA website + invitation
- Consideration of responses → finalisation and publication of final guidance
- Regulatory aspects to be determined
 - The equivalent pharmacovigilance guidance is included in the *Therapeutic Goods Regulations 1990*
 - Conditions of registration

Questions?



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