Overview

• Infectious disease safety risk of therapeutic goods
• Risk assessment and risk management
• Section 14 and 14A Exemption
• Epidemiological situations and surveillance reporting
• Donor Suitability
TGA takes a risk-based approach to infectious disease safety for all therapeutic goods:

- Medicines (plasma derivatives, recombinant proteins)
- Medical devices
- Biologicals
Essentially the risks are the same:

- Human or animal derived materials may contain infectious disease agents
  - Prions, viruses, bacteria (including mycoplasma), parasites that, when transferred into a recipient, may cause disease
Risk scenario – Cell/tissue

Donor is infected with an agent capable of causing disease

Infectious agent is present in donated cells/tissues

Infectious agent survives the manufacturing process

Infectious agent is transferred into recipient

Agent infects recipient causing harm
Risk assessment

- **What could go wrong?**
  - Risk identification

- **How serious could harm be?**
  - Consequence assessment

- **How likely is it?**
  - Likelihood assessment

- **What is the level of concern?**
  - Risk evaluation
Risk assessment process

• What could go wrong?
  – Establish risk context e.g.:
    ▪ Data/evidence for risk; data gaps
    ▪ Epidemiological data
    ▪ Existing regulatory requirements/controls
    ▪ Type of cell/tissue therapy
    ▪ Public perception/acceptability of risk
    ▪ How uncertainty is managed
  – Identify risks that may warrant characterisation
Risk assessment process

• How likely is harm to occur?
  – Prevalence and incidence in population
  – Vaccination history
  – Evidence of transmission
  – Viral loads
  – Infectious dose
  – Survival of infectious disease organism under relevant conditions
  – Donor recipient relationship (1:1 or 1:1000)
Risk assessment process

• How serious is the harm?
  – Are there subsets of the population more susceptible to infection?
  – What is the level of immunity in the population?
  – Are there treatment options available?
Risk assessment process

• What is the level of concern?
  – Estimate level of risk
  – Identify risks that require management
Risk management

- Donor Suitability
- Donor Testing

- In process testing
- Optimize sampling
- Validated product testing

- Surveillance
- Biovigilance
- Re-evaluation of risk
- Post-donation information

- Pathogen reduction measures
- Manufacturing Steps to remove or inactivate adventitious agents

Prevent
Detect
Monitor
Remove
Risk management - limitations

• Donor screening – donor compliance, appropriate questions to identify donors at risk, donor may be asymptomatic
• Donor testing – availability of appropriate test, window period donations and the cost
• Pathogen reduction measures – ability of the manufacturing process to inactivate/remove infectious disease agents; may affect quality of the cells/tissues
Choosing a risk management option

- Sometimes the only feasible option is additional donor screening e.g. no approved tests, no pathogen reduction possible
- Donor testing – supplementary tests
- Alternatively, if there are no additional questions that can be asked or donor testing is not possible, in process testing or pathogen reduction may need to be considered e.g. validated PCR based testing or irradiation
Choosing a risk management option

- Testing: supplementary donor testing or in-process testing using advance molecular based testing (validated) of the starting material
- Pathogen reduction may be the best option to manage multiple significant pathogens at once
- Reduce consequences to recipient – vaccination or treatment
Risk management and legislated standards

- Non-compliance to legislated standards
  - Consent under Section 14 of the Act may be possible to allow supply of therapeutic goods that do not comply with Standards
- TGO’s can be amended and have sunset dates (usu. expires in 10 years) – allows re-evaluation of the standard;
- Approved exemptions help addressing specific issues which can be rolled into TGO’s when they are re-evaluated
Section 14 and 14A Exemption*

• It is an offence to import, supply or export therapeutic goods that do not comply with a standard applicable to the goods, unless the prior consent in writing of the Secretary has been given (see section 14 the Therapeutic Goods Act 1989) or a civil penalty may be payable (see section 14A of the Act).

• A S14 application can include goods in multiple ARTG entries provided:
  – the goods have the same active ingredient;
  – all the issues in relation to granting consent are the same for all the goods, and
  – the non-compliance in relation to the goods relate to the same part or parts of a standard applicable to the goods.

What information must be provided?

• The applicant should provide information:
  – identifying the relevant part of part (or parts) of the standard that is not complied with;
  – the relevant product/s (scope);
  – the circumstances giving rise to the non-compliance;
  – the risks associated with the non-compliance and steps being taken to address any such risks (for instance, an alternate risk reduction measure);
• The TGA may request additional information in order to come to a view about an application.
Question: Malaria acceptance criteria: What would need to change for the TGA to be able to accept a group submission?

- TGA has provided advice to BAA*
- Scope – list products should be specified
- Rationale and risk assessment
- Literature evidence and international practice
- Risk reduction measures for example:
  - Additional questions/testing
  - In-process testing (Validated for the product)
  - Tissue processing (Irradiation, freezing)
  - Recipient screening and treatment

* Teleconference with BAA on 19 September 2019 (Debbie Stracey) and the ETAC meeting in May 2019.
Question: Feedback regarding the suitability of the EREEID surveillance documents for the purposes of TGO 88 Table 1 (s) ?

- TGA is supportive of centralised procedures (EREEID surveillance) for monitoring and initially assessing relevant infectious disease outbreaks.
- It is the responsibility of tissue banks to demonstrate that processes are in place to identify, monitor, assess and action epidemiological situations relevant to their products:
  - Risk assessment that identifies whether an infectious disease outbreak is relevant to the quality (infectious disease safety) of the cells/tissue
  - Process to link monitoring information to any action taken (e.g. interim instruction/permanent deferral or supplementary testing)
  - Risk management needs to specified by each bank i.e. What is done to mitigate the identified risk and how ?
Managing epidemiological situations

• Sponsors that want to utilise these procedures (once finalised) will be required to submit a **variation** to their biological entry and include these procedures into their product dossier;
• Implementation of the procedures and any donor deferrals **would not require a variation**, but do need to be informed to the TGA.
• TGA would like each sponsor of biologicals to notify of their actions (including no action)
  – **To see how procedures for epidemiological situations are being implemented by each sponsor**
  – **To ensure consistency in approach for the same cell/tissue types**
Question: Epidemiological situations and surveillance reporting: what would the TGA expect of Tissue Banks in response to a moderate or high risk threat assessment?

- Table 1 (s) of TGO 88 requires that ‘A donor with exposure to particular epidemiological situations’ is subject to a deferral period ‘consistent with the epidemiological situation’:
  - Action taken (e.g. interim instruction or permanent deferral or testing)
- ‘Deferral procedures and parameters for particular epidemiological situations should be informed’ to the TGA
- This criterion is intended to cover unforeseen infectious disease risks in donors:
  - Domestic disease outbreaks (e.g. Dengue)
  - International disease outbreaks (e.g. Zika, Ebola)
Question: Donor Suitability: Insulin history of potential donors, if full history is not available or insulin was not listed on the ARTG?

- Quality of insulin and potential risks to be considered:
  - Received overseas or imported non-ARTG insulin?
  - Manufacturers producing bovine or porcine insulin for sale in foreign countries do not have to comply with TGA requirements;
  - Possible threat of bovine spongiform encephalopathy (BSE) or "mad cow disease" transmission through the use of bovine insulin if it is derived from tissues contaminated with the BSE agent

- Case by case risk benefit clinical decision as per TGO 88 9 (13)
- Rational for donor acceptance must be recorded as per TGO 88 9 (13)(a)
Question: How to determine if porcine derived insulin contained viable non-human animal cells or tissues?

• How to establish the quality of insulin used by the donor?
• ARTG listed porcine derived insulin must demonstrate quality:
  – Compliance with the quality standards (e.g. Ph Eur Monograph 1638)
  – Sterility and endotoxin safety
  – Infectious disease safety* of porcine derived insulin:
    ▪ Mycoplasma, Viral and Prion (BSE) risks;
    ▪ BSE cross contamination: if it is manufactured in the same facility as bovine insulin and adequate provisions to prevent cross-contamination are lacking.

Question: Why continue with requiring a 5 year exclusion for IV drug use if detection periods are far shorter for current mandatory transmissible diseases?

International Status:

  - Any History of injectable drug abuse = **permanent deferral**
- **United States** – Indefinite deferral for a ‘Lifetime use of a needle to inject non-prescribed drugs (including steroids)’
- **Canada** – Indefinite deferral for ‘Intravenous use of illegal street drugs/narcotics’
- **New Zealand** - If the donor has ever injected, even once, drugs not prescribed by a doctor, defer permanently
- **Netherlands** – Indefinite deferral for ‘Ever injected drugs or regular partner has injected drugs’
- **Sweden** – Indefinite deferral for ‘intravenous drug abuse’
- **Denmark** – Indefinite deferral - Lifetime IDU (‘a single injection many years ago is enough’)
Injecting drug use review in Australia - 2017

- A systemic review of blood donor deferral for injecting drug use was undertaken by an expert committee in Australia*
- Looked at the available evidence, conducted risk analysis to consider window period risks, mathematical modelling and international practices
- Review committee recommended five year deferral policy for IDU (consistent with TGO 88)
