Risk-based approach to infectious disease safety

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The TGA applies 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
Which infectious agents do we need to do something about?

This can be determined by risk assessments…
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

• What could go wrong?
  – Only risks with a **plausible** pathway to harm need further characterisation
  (Is there a rate limiting step in the pathway?)
Example of pathway to harm

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 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
The TGA is establishing a systematic approach to risk assessment based on the principles of the international standard ISO 31000.
A systematic risk assessment approach allow us to:

• Identify and document critical factors/data relevant at the time
• Provide a transparent record of risks and their management
• Allow for comparability across different organisms
• Provide a basis for assessment of new information
A systematic risk assessment approach allows us to:

• Allow for review of the appropriateness of risk management measures
  – Review of TGO 88

• Allow modelling of epidemiological situations and the effect they would have on the level of risk
Systematic approach to risk assessment

Defining criteria for:

• Likelihood
• Consequences
• Risk estimates
• Levels of risk that require action
### Example likelihood criteria

<table>
<thead>
<tr>
<th>Likelihood of harm</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Highly unlikely</td>
<td>Harm may occur only in very rare circumstances</td>
</tr>
<tr>
<td>Unlikely</td>
<td>Harm could occur in some limited circumstances</td>
</tr>
<tr>
<td>Likely</td>
<td>Harm could occur in many circumstances</td>
</tr>
<tr>
<td>Highly likely</td>
<td>Harm is expected to occur in most circumstances</td>
</tr>
</tbody>
</table>
## Example consequence criteria

<table>
<thead>
<tr>
<th>Level of harm (consequences)</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marginal</td>
<td>Ailment not requiring medical treatment</td>
</tr>
<tr>
<td>Minor</td>
<td>Minor illness/injury requiring medical treatment</td>
</tr>
<tr>
<td>Intermediate</td>
<td>Serious illness/injuries usually requiring hospitalisation; treatment is usually available; prevention may be available</td>
</tr>
<tr>
<td>Major</td>
<td>Deaths or life-threatening illness/injuries; treatment or prevention is not usually available</td>
</tr>
</tbody>
</table>
# Example risk estimate matrix

<table>
<thead>
<tr>
<th>LIKELIHOOD ASSESSMENT</th>
<th>RISK ESTIMATE</th>
<th>CONSEQUENCE ASSESSMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Highly likely</td>
<td>Low</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>Likely</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>Unlikely</td>
<td>Negligible</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
<td>Moderate</td>
</tr>
<tr>
<td>Highly unlikely</td>
<td>Negligible</td>
<td>Negligible</td>
</tr>
<tr>
<td></td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
<td>Moderate</td>
</tr>
<tr>
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<td></td>
<td>Intermediate</td>
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</tr>
</tbody>
</table>

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*Note: This matrix provides a general framework for assessing risks and consequences. The specific definitions for each level (Low, Moderate, High, Negligible, etc.) may vary depending on the context and the specific risk assessment criteria.*
### Example risk estimate categories

<table>
<thead>
<tr>
<th>Estimate of risk</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Negligible</strong></td>
<td>Risk is of no discernible concern and there is no present need to invoke actions for mitigation.</td>
</tr>
<tr>
<td><strong>Low</strong></td>
<td>Risk is of minimal concern, but may invoke actions for mitigation beyond standard practices.</td>
</tr>
<tr>
<td><strong>Moderate</strong></td>
<td>Risk is of marked concern and will necessitate actions for mitigation that need to be demonstrated as effective.</td>
</tr>
<tr>
<td><strong>High</strong></td>
<td>Risk is of considerable concern that is unacceptable unless actions for mitigation are highly feasible and effective.</td>
</tr>
</tbody>
</table>
Now that we have identified the infectious agents we need to do something about…

What do we need to do about them?
Risk management

• What are the outcomes of the risk evaluation?
• What measures are available for managing risk?
• How effective are the risk management measures?
• How feasible, practical or compatible are the risk management measures?
• Do the risk management measures themselves introduce new risks or exacerbate existing ones?
Risk management - options

• There are currently 3 main options for management of infectious disease risks of blood, cells and tissues. All are aimed at reducing the likelihood
  – Donor screening
  – Donor testing
  – Pathogen reduction measures
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
• 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
- Alternatively, if there are no additional questions that can be asked of a donor, testing or pathogen reduction may need to be considered e.g. HBc testing for HBV occult infection
Choosing a risk management option

- Pathogen reduction may be the best option to manage multiple significant pathogens at once
- Reduce consequences to recipient – vaccination or treatment or
- Accept the level of risk
Responses to infectious disease safety questions for TGA
Questions for TGA

Is there a timeline for review of TGO 88 and what areas do you think you may target in such a review specifically?

- At this stage there is no definite timeline for the review of TGO 88, nor is there a definitive scope of the review.
- The Biological Science Section of TGA has just begun to collect our experiences in evaluating blood, cells and tissues against TGO 88.
- This, together with specific feedback from stakeholders, will be used to inform the future review.
Can you comment on the IVD framework inhibiting the implementation of testing for emerging, re-emerging and emerged diseases? i.e. Do you think the framework precludes implementation of testing for diseases such as common Australian arboviruses?

• The framework does not preclude implementation of testing for diseases such as arboviruses providing laboratories comply with the requirements (or seek an exemption).

• Currently, any test for the detection of a transmissible agent for donor screening purposes is a Class 4 IVD (or Class 4 in-house IVD)

• If a commercial test is unavailable in Australia laboratories may apply for an exemption to import a device that is approved for use overseas
Can you comment on why malaria featured so highly in TGO 88, while common Australian arboviruses, which affect significantly greater proportions of the population were not?

• Malaria causes significant harm and donors may be infectious for some time
• TGO 88 criteria are consistent with International requirements
• Malaria criteria are intended to identify potential donors who have come from or travelled to malaria endemic areas
• Banks may choose to impose additional criteria to identify donors who may be at risk of infection with arboviruses (Table 1 (r) and (s) of TGO 88). The additional criteria should be the result of a risk assessment.