Devices Sponsor Information Day

UNDERSTANDING THE TGA’S REGULATORY FRAMEWORK

SUPPORTING ORGANISATIONS —

www.sponsor-day.org
Conformity Assessment

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Presentation overview
Conformity Assessment basics
Common questions
Common data omissions
Questions and answers
What is Conformity Assessment?

Procedures used and evidence generated by the manufacturer to demonstrate that a medical device is designed and produced to be safe, fit for purpose and perform as intended.
EU and Australian CA requirements

Global Harmonization Taskforce (GHTF) → now International Medical Device Regulators Forum (IMDRF)

EU adopted a medical device regulatory system based on GHTF principles >20 years ago

Australia more recently adopted new regulatory frameworks based on GHTF:
• medical devices in 2002
• IVDs in 2010
EU and Australian CA requirements

• Common basis (GHTF principles) means EU and Australian requirements are very similar
• TGA even issues European certificates for some medical devices
• Some examples of where requirements differ…
  – Microbial origin
  – Definition of Central Circulatory System
  – Definition of ‘Active’ devices
Supply of medical devices in Australia

• Majority of devices are supplied in Australia under EC certification.

• Some high risk devices must hold TGA issued conformity assessment certification in order to be supplied in Australia…
## TGA Conformity Assessment required

<table>
<thead>
<tr>
<th>For a device that…</th>
<th>Regulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contains tissues of animal origin (non-viable)</td>
<td>4.1(a)</td>
</tr>
<tr>
<td>Contains tissues, cells or substances of microbial or recombinant origin</td>
<td>4.1(b)</td>
</tr>
<tr>
<td>Contains stable derivatives of human blood or human plasma</td>
<td>4.1(c)</td>
</tr>
<tr>
<td>Incorporates a substance that is considered to be a medicine</td>
<td>4.1(d)</td>
</tr>
<tr>
<td>Is a Class 4 IVD or Class 4 in-house IVD</td>
<td>4.1(e)</td>
</tr>
</tbody>
</table>
When is TGA Conformity Assessment Required for an IVD?

• Most manufacturers/sponsors choose to use overseas certification to support ARTG inclusion unless supplying Class 4 IVDs
  • EU Certificate, Canadian License, ISO13485

• A manufacturer MUST undergo TGA Conformity Assessment in order to supply any Class 4 IVD.
  • In-house Class 4 IVDs – same applies to laboratory

A manufacturer may choose to undergo TGA Conformity Assessment at any time for other classes of IVD products

It is no longer mandatory for Australian IVD manufacturers to undergo TGA Conformity Assessment*

*Medical Device Reforms implemented in 2014
What is CA of a medical device?

1. **Risk based classification system**
   - Classification determines minimum CA procedure(s)

2. **Conformity Assessment Procedures**
   - CA procedure(s) applied by manufacturer to generate evidence that medical device complies with EPs

3. **Essential Principles**
Benefit versus risk approach

Device classification is based on consideration of:

- Risk to patients, users and other persons (probability and severity of harm)
- Degree of invasiveness in the human body
- Intended use of the device
- Duration of use

Risk classification is based on:

- Intended use of the device
- Duration of use
- Degree of invasiveness in the human body
- Risk to patients, users and other persons (probability and severity of harm)
What does this mean for the medical device manufacturer?

• Regardless of the medical device risk classification and conformity assessment procedure applied, the manufacturer needs to ensure that they have met the applicable essential principles for their device.

• The manufacturer should ensure that there is a technical file that describes the product. Intended purpose, risk classification, and standards applied to the device to ensure that the applicable requirements of the essential principles are met.

• The technical file is a living document – this means that depending on the requirements of the standards applied to the device, the manufacturer will have to ensure that validation and supporting documentation are updated to ensure ongoing compliance with the essential principles.
What is Benefit v Risk for a Class 4 IVD?

Benefit v Risk – Public and Personal risk

A class 4 IVD represents the greatest risk to public health should an erroneous result occur.

**Detection** of transmissible agents posing a high public health risk
- Screening and Diagnosis
- Blood, organ and tissue donations
- Examples: HIV, Hepatitis C, Syphilis, H1N1

**Detection** of red blood cell antigens and antibodies and non red cell typing
- Blood typing – but only for specific markers
- ABO, Rh, Kell, Duffy, Kidd
Conformity Assessment basics

Medical Device Manufacturer

Conformity Assessment Body / TGA

Output

CA Procedures

QMS

EPs

Review

On-site inspection

Technical file review

Manufacturer’s evidence

TGA or EC certificate
CA process work flow

1. eBS CA application form
2. Supporting information
3. Pre-assessment & assessment plan
4. Assessment fees
5. ACMD (optional)
6. Assessment
7. Decision
8. Certificates
CA process – Pre-assessment

- Screening
- Application effective
- Assessment Plan
- Fees
Fees

• Each application may involve multiple fees:
  – CA application fee +
  – Quality system assessment fee +
  – Additional inspection costs (e.g. travel costs) +
  – Design/Type exam assessment fee for each kind of device (UPI)

• Fees for assessment of changes, reviews & surveillance assessment fees also apply during life of certificate
Conformity Assessment - Elements

The Conformity Assessment Procedures require the following elements:

- **Quality Management System**
  - Quality management system in compliance with ISO 13485 (except for Class I devices)

- **Post market surveillance**
  - Surveillance of product performance in the market

- **Technical documentation**
  - Technical documentation for the design of the device. Evidence of compliance with Essential Principles.

- **Declaration of Conformity**
  - Declaration that the device complies with the regulatory requirements
Conformity Assessment – QMS elements

Part 1
Full Quality Assurance
Design & Development
Production Validation
Final Inspection

Part 4
Production Quality Assurance
Production Validation
Final Inspection

Part 5
Product Quality Assurance
Final Inspection

Conformity Assessment
Conformity Assessment - Design

Commonly referred to as the Technical File or Design Dossier

- Cover Letter
- Table of contents
  
  Refer IMDRF website for guidance
- Supporting data
TGA Medical Device Conformity Assessment – QMS

• For devices that contain tissues of animal/microbial origin or incorporate a medicine, TGA will conduct assessment of the QMS. This may be an on site inspection of the manufacturing facility, and in some cases critical suppliers.

• TGA’s review of the QMS (ISO 13485) demonstrates that the manufacturer has procedures in place to ensure that the product can be made consistently through adequate
  • supplier controls - supplier QA, purchasing control
  • process controls - Internal audit, validations
  • Post market surveillance to ensure that any feedback is considered in the continuous improvement of the product
  • Change controls.

• As well as the usual QMS elements there will be a particular focus on supplier quality assurance and validation of any special processes required to manufacture a combination device.

• The result of TGA’s assessment of the manufacturer’s QMS is a conformity assessment certificate issued to Schedule 3 Part 1 – Full Quality Assurance Procedures, Schedule 3 part 4 Production QA or Schedule 3 part 5 Product QA.
Design Examination - what does this mean for the manufacturer?

- A design dossier is a snapshot in time of the device technical file.
- The design dossier is presented to the conformity assessment body to demonstrate that the product meets the requirements of the Essential Principles.
- The Design Dossier should describe the device, intended purpose and contain information to verify and validate the design of the device. This can be done by compliance to standards:

  E.g. if the device is sterilised by ETO, the dossier will contain a sterilisation validation test protocol and report to ISO 11135.

  Or if the device is required to be biocompatible - the manufacturer may choose to apply ISO 10993.
## Design Dossier Review (Part 1.6)

- Part 1 Full Conformity Assessment Procedure
- Part 1.6 – Design Review
  - Class 4 IVDs

<table>
<thead>
<tr>
<th>Overview of Required Information</th>
<th>Level of Detail</th>
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<tbody>
<tr>
<td>Device description including variants</td>
<td>Address each point</td>
</tr>
<tr>
<td>Device description</td>
<td></td>
</tr>
<tr>
<td>Reference to previous device generation – not yet available on any market</td>
<td>SUMMARY</td>
</tr>
<tr>
<td>Device history – already available on the market in another jurisdiction</td>
<td>SUMMARY</td>
</tr>
<tr>
<td>Risk analysis and control</td>
<td>DETAILED</td>
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<tr>
<td>Design and manufacturing information</td>
<td></td>
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<tr>
<td>Device design</td>
<td>DETAILED</td>
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<tr>
<td>Manufacturing processes</td>
<td>SUMMARY</td>
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<tr>
<td>Design and manufacturing sites</td>
<td>SUMMARY</td>
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<tr>
<td>Product validation and verification</td>
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</tr>
<tr>
<td>Specimen type</td>
<td>DETAILED</td>
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<tr>
<td>Accuracy – Trueness</td>
<td>DETAILED</td>
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<tr>
<td>Precision – Reproducibility and Repeatability</td>
<td>DETAILED</td>
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<tr>
<td>Traceability of control and control materials</td>
<td>DETAILED</td>
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<tr>
<td>Analytical sensitivity</td>
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<tr>
<td>Analytical specificity</td>
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<tr>
<td>Measuring range of the assay</td>
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<td>Validation of assay cut-off</td>
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<tr>
<td>Stability</td>
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<tr>
<td>Claimed shelf life</td>
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<tr>
<td>In use stability</td>
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<tr>
<td>Shipping stability</td>
<td>DETAILED</td>
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<tr>
<td>Software</td>
<td></td>
</tr>
<tr>
<td>Clinical evidence</td>
<td>ELABORATED</td>
</tr>
</tbody>
</table>
Obligations once certified

- Substantial changes
- Ongoing surveillance inspections
- Certificate reviews, e.g. conditions or regulatory reviews
- Post market reporting
- ARTG inclusions for supply
Common questions

New versus change applications
Substantial changes
Abridged assessment
New vs Change applications

**New**
- New QMS certification (manufacturer does not hold any current TGA QMS certification)
- ‘Upgrade’ of conformity assessment procedure, e.g. Part 4 Production QA to Part 1 Full QA
- Design examination for a new UPI

**Change**
- Change to QMS as previously certified
- Change to design of an existing UPI
Substantial changes

- Legislation does not contain a definition for “substantial change”
- Recommended that manufacturers have a system for categorising changes as substantial and notifiable to TGA or not.
- At minimum, changes to any detail on the CA certificate itself constitutes a substantial change.
Substantial changes - QMS

- New manufacturing facility
- Manufacture name and/or address change
- Critical process change
- Change to critical suppliers
- New devices
Substantial changes – Device

- Change to packaging
- Change to materials
- Additional variants
- Change to intended performance
- Shelf life

• Evidence of on-going compliance to the Essential Principles
How does a manufacturer determine what should be notified?
Have a change assessment process

- Manufacturer may have a change assessment process to work out if a change is significant and notifiable to TGA or other regulatory authorities.

- The process may ask a series of questions such as:
  - Does the change introduce new hazards/risks?
  - Does the change alter the intended use and/or compliance with the EPs?
  - Does the change affect clinical performance?
  - Does the change require the device to undergo further validation?
  - Does the change mean the device will be used on different users?
How to assess change for an IVD?

**QMS**
- Similar to medical devices, e.g. certificate information, change to critical suppliers

**Device**
- Specific IVD Essential Principles which must continue to be met
  - Does a change to the Intended Use introduce potential new risks?
    - Eg, Diagnosis to Screening, Addition of sample type
  - Does IVD continue to meet required Specificity and Sensitivity, i.e. Intended performance?
  - Does a change to a self-testing IVD increase risk or complexity for the user?
  - For immunohaematology only – addition of a variant
Abridged CA assessment

1. **Process**
   - Written request
   - Provide supporting evidence

2. **Eligibility**
   - Dependent on level of assessment required
   - Applicants should be prepared to pay scheduled fee

3. **Guidance available**
   
Supporting Data – common omissions

Risk management documentation
Clinical evidence
GMP evidence for incorporated medicinal substances
Risk management

• Risk management file should include:
  – Risk analysis relevant to design, use and production of device:
    ▪ FMEAs,
    ▪ risk/benefit analysis
    ▪ residual risks and overall risk evaluation
  – Documentation required to interpret this, i.e. definitions of risk levels and acceptability criteria
Clinical evidence

• Essential Principle 14:
  – Every medical device requires clinical evidence to demonstrate compliance with the EPs

• As per Schedule 3, Part 8

• Session later in the day!
Medicinal substances

- GMP Evidence for incorporated medicinal substances
- EP 7.4 – Verification of incorporated substance
- Assessment generally focused on:
  - Verification of the safety and quality of the substance (GMP, DMF)
  - Verification of the ancillary action of the substance
- Levels of assessment depends on the situation
What does benefit vs risk mean for a medical device?

- **ISO 14971 - Medical devices -- Application of risk management to medical devices (including IVDs)**
- A manufacturer needs to have evidence that a risk management process has been applied to the design and manufacturer of the device.
- A risk management report is the summary of the process and may include details of a specific risk analysis method, and how identified risks have been mitigated through design, manufacturing process controls or labelling.
- The manufacturer is required to demonstrate that the benefits of using the device outweigh the risks.
Potentially problematic supporting data for an IVD

Risk Management Report
- Living Document
- Risk Management - File v Report
- Detailed v Summary

Clinical Evidence Report
- Will be discussed in detail in next session
- Clinical Performance
- Clinical Expert
Questions
Australian Government

Department of Health

Therapeutic Goods Administration