Devices Sponsor Information Day

UNDERSTANDING THE TGA’S REGULATORY FRAMEWORK

SUPPORTING ORGANISATIONS —

www.sponsor-day.org
Post-market: adverse events and monitoring activities

Session Chair —
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Chief Executive Officer, Australian Dental Industry Association

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Chief Executive Officer, Brandwood Biomedical

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RA QA Affairs & IBP Manager, Abbott Diagnostics
Post-market

Post-market adverse events and monitoring activities

Pam Carter
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Medical Devices Branch
Devices Sponsor Information Day 2015

15 October 2015
Overview

- The TGA’s Role in post market vigilance and monitoring
- Post-market regulation 101
- Adverse events and reporting
  - What is an adverse event
  - What, when, how to report
  - Issues to avoid
  - What happens to a report
  - Outcomes
- Post-market monitoring
  - What does a post market review look like
  - Ensuring you get the what, when, how right
  - Annual monitoring
Role of the TGA in market vigilance and monitoring

The TGA’s role is to continually monitor and evaluate the safety and efficacy or performance of therapeutic goods that are available on the market and to manage any risks associated with individual products.
Post-market regulation 101

- Post-market regulation of devices is monitoring to ensure the device continues to be “free from unacceptable risk”

- At all times the supplier & manufacturer must demonstrate continued compliance with “essential principles” that describe the safety & performance of a medical device

TGA has the authority to….

- Ask questions of sponsors and manufacturers
- Seize products & inspect premises
- Cancel/suspend products from supply

Manufacturer/Sponsor is obliged to gather and report certain information
Adverse events and reporting

Mr Smith’s blood glucose reading according to his glucose monitor was high yet he went into hypoglycaemic crisis and required hospitalisation

• Is this an adverse event?
• And, if so, does anyone need to know about it?
Adverse events

What is an adverse event?

Events involving medical devices that have resulted in, or could have resulted in, serious injury to a patient, health professional or other person are reportable.

What is ‘serious’?

– also known as serious deterioration in state of health
– a life threatening illness or injury
– a permanent impairment of a body function
– permanent damage to a body structure, or
– a condition necessitating medical or surgical intervention to prevent permanent impairment of a body function or permanent damage to a body structure.
What, when, how to report

So having decided that the event meets the reporting criteria; when, how and what to report.

• Within **two days** if it is a serious public health threat
• Within **ten days** of you becoming aware of a death or serious injury.
• Within **thirty days** of you becoming aware of an event that might have led to serious injury or death.

**When in doubt it is better to report than not to report.**
Are there issues to avoid when reporting?

- ARTG entry number - what is it?
- Proof reading – check accuracy, be careful of cut and paste
- Lack of information or relevancy
- Duplicates – ensure all parties in your company are aware of what has already been sent to the TGA
- Similar event rates
- Ensure you provide follow-up or final reports in a timely manner

Further information on how to fill in the report can be found in the FAQs on the TGA website.
What happens to reports?

Initial risk assessment...

- All reports are entered into the Scheme’s database
- Urgent reports are addressed immediately by the Scheme coordinator
- Focus is on unusual problems, potentially serious problems, or problems that have high levels of incidence
  - Also inaccurate/missing/incorrect reporting of adverse events
- The TGA investigator contacts the sponsor (company) and works with them to resolve any issues
- Reports are treated as confidential
- Most reports are placed onto the Database of Adverse Event Notifications (DAEN). This occurs three months after receipt of the final report.
Outcomes of investigations

The investigation by TGA and the sponsor/manufacturer of Mr Smith’s adverse event reveals that the problem was due to a software error that switched the units of measure from mmol/L to mg/dL. What should the outcome be?

If action is necessary it may involve any of the following:

- **Recall** - removal of goods from sale or use, or for correction
- **Safety Alert** - urgent information to inform those using the device, or affected by the problem
- **Report** in the TGA News, TGA website or other appropriate journal/s.
- **Product improvement**
- **Referral to other TGA Sections** for regulatory action.
The Outcome to the report about Mr Smith’s BG Monitor

- The software error occurred when:
  - the blood glucose tests strips used were purchased from overseas; and
  - The user clicked ‘yes’ when asked if they wanted to use these particular test strips
- This was the 20th report in the last year - there were 10 other hospitalisations and one death
- The manufacturer developed software that prevented test strips from changing the measurement setting
- A recall was initiated to exchange monitors that had the “faulty” software
Post-market Monitoring

- There have been a number of adverse events for a particular heart valve. The events are mostly to do with leaflet breakage.
- During an investigation of the latest report, a report for the same problem was received for another manufacturer’s heart valve.
- This should be a rare problem therefore the TGA checks what data it has and what else is known about this problem.
- The review revealed that there have been a small number of reports for other heart valves and a recall for another manufacturer’s heart valve.
- A review of all similar heart valves was commenced to determine if there is an issue with one particular valve or there is something else going on.
What does a post-market review look like?

• **Why are post-market reviews conducted** (this is not an exhaustive list):
  - Trends from the Medical Device Incident Report Investigation Scheme
  - Recurrent breaches of the Advertising Code
  - Unresolved/repeated recalls
  - Information received from other regulatory agencies

• **Who or what is reviewed:**
  - Sponsor
  - Manufacturer
  - Ingredient
  - Product
  - Kind of Device

• **When:**
  - Reviews for safety and performance may be conducted at any point in the product’s life-cycle.
Post-market review process (cont.)

• How:

Calling in and reviewing:

- Labels
- IFU
- Advertising material
- Technical documentation
- Declaration of Conformity and certification
- Risk assessment
- Ingredients and formulations
- Post market data such as the number of problems, complaints, adverse events that have been reported
- Clinical evidence

Dependent on the issue under review
Key elements to ensuring you get the what, when and how right

• Provide all information requested and just the information requested
• Present the information in a logical, clear format
• Link the information – literature search and post market data
  Clinical Evidence Report ➔ Risk Assessment ➔ Risk mitigations
• Clinical Evidence
• Getting the numbers right
• Referencing that is organised and cross referenced in the submission
• Identify all probable and potential risks
The tale of the problem heart valve

- **Information recalled in:**
  - Clinical evidence
  - Technical documentation
  - Risk assessment documents
  - IFUs
  - Post market data

- **What was sent:**
  - Multiple emails with lots of journal articles
  - IFUs
  - EP checklist
  - Risk assessment

- **When was it sent:**
  - Following a reminder s41JA letter
  - Emails stretched across a week or more

So, what happened next?
What happened next?

- The TGA wrote a letter Proposing to Cancel (s41GN(2)) the ARTG of the heart valve because:
  - The Sponsor failed to provide information after a s41JA letter (s41GN(1)(c)); and
  - The Sponsor failed to comply with the Conditions of Inclusion (s41GN(1)(b));
    - Must have sufficient information to demonstrate compliance with the Essential Principles; and must provide the information when requested to do so by a delegate of the Secretary
    - And because the safety and performance of the device is unacceptable (s41GN(1)(d))
- The sponsor's response failed to alleviate TGA's concern about the safety and performance of the device
- A letter Cancelling the device based on the above three provisions
- The cancellation was published on TGA's website
# Results of 2014 Reviews

## Sponsor cancelled

<table>
<thead>
<tr>
<th>Reason</th>
<th>Number</th>
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<tbody>
<tr>
<td>Change of sponsor</td>
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</tr>
<tr>
<td>Change in manufacturer</td>
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</tr>
<tr>
<td>No device supplied under entry</td>
<td>5</td>
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<tr>
<td>Device no longer supplied</td>
<td>6</td>
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<tr>
<td>Information not provided</td>
<td>11</td>
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<tr>
<td>Incorrectly classified</td>
<td>1</td>
</tr>
<tr>
<td>Model superseded</td>
<td>2</td>
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<tr>
<td>No longer the distributor</td>
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## TGA Cancelled

<table>
<thead>
<tr>
<th>Reason</th>
<th>Number</th>
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<tbody>
<tr>
<td>Not replying to a s41JA request for information</td>
<td>5</td>
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<tr>
<td>Non compliance with automatic conditions of inclusion</td>
<td>6</td>
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</table>
Annual monitoring of high risk medical devices

- The TGA also reviews marketed devices for any safety signals by requesting supply, complaint and adverse event data for the first three years after inclusion.

- **Why**
  - Ensure that devices new to the Australian market are continuing to meet the essential principles for safety and performance.
  - Ensuring that the sponsor and manufacturer’s post market surveillance system is functioning sufficiently to detect any issues as early as possible.
Annual monitoring of high risk medical devices

In addition to reporting adverse event reports the TGA requests information about high risk devices every year. High risk medical devices are:

- AIMD
- Class III
- Implantable Class IIb
- Class 4 IVDs

What information is required:
- Complaints, adverse events and number supplied
- Reports should be for the period 1 July to 30 June

When to you provide it:
- 1 October each year

How to provide it:
- Electronically
- In a table format
Key messages

• **Adverse Event Reporting**
  – Timeliness – Of initial report and of responses to further questions from the TGA
  – Accuracy/Relevance – Provide all key identifying and descriptive information – Beware of cutting and pasting from previous events that may be irrelevant
  – Provide incidence rates

• **Post-market Monitoring**
  – Read the request for information carefully – Provide considered answers to the questions, making links between the information provided and the issue being explored
  – It is the manufacturer's responsibility to put two and two together

• **Annual monitoring**
  – Be timely - the reports are all due in October of each year. Don’t rely on TGA reminders
  – Provide an argument for the notion that the figures demonstrate acceptable safety and performance.
  – Learn from the information that you are submitting
Postmarket for Devices – are You Prepared?

Arthur Brandwood
CEO – Brandwood Biomedical

Devices Sponsor Information Day – 15 October 2015
On Registries and Regulators

## Hip and Knee Arthroplasty

### Table HT49: Yearly Usage of Individual Primary Conventional Total Hip Prostheses identified as having a higher than anticipated Revision Rate

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<td>Elite Plus/Charnley LPW</td>
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<td>29</td>
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<td>Elite Plus/Apollo</td>
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<td>9</td>
<td>16</td>
<td>17</td>
<td>10</td>
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<tr>
<td>H Moore/Mueller</td>
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<td>5</td>
<td>9</td>
<td>5</td>
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<tr>
<td>* Margron</td>
<td>0</td>
<td>28</td>
<td>56</td>
<td>130</td>
<td>123</td>
<td>140</td>
<td>96</td>
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<td><strong>Artek</strong></td>
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<td><strong>Inter-Ops</strong></td>
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<tr>
<td><strong>Re-identified and still used</strong></td>
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<tr>
<td>FZL Multimeck/Delta</td>
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<td>0</td>
<td>10</td>
<td>62</td>
<td>28</td>
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<td>0</td>
<td>0</td>
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<td>11</td>
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<td><strong>SPH-Blind</strong></td>
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<td>262</td>
<td>204</td>
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<td>49</td>
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<td><strong>Newly Identified</strong></td>
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<tr>
<td>Coral/ASR</td>
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<td>0</td>
<td>25</td>
<td>296</td>
<td>551</td>
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<tr>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>7</td>
<td>41</td>
<td>52</td>
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<td><strong>Anca_Fit</strong></td>
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<td>9</td>
<td>21</td>
<td>50</td>
<td>66</td>
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<td>* Hayes Consensus</td>
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<td>1</td>
<td>15</td>
<td>38</td>
<td>70</td>
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<td>36</td>
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<tr>
<td>* Lyderic II (cemented)</td>
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<td><strong>Bionik</strong></td>
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<td>0</td>
<td>0</td>
<td>0</td>
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</tr>
</tbody>
</table>

Note: * Femoral Components  
** Acetabular Components
Then TGA asks 9 Questions...

1. The Australian Register of Therapeutic Goods (ARTG) Number for the device.

2. A summary report of the number and types of problems, complaints and adverse events that the sponsor and manufacturer have received in relation to the implant. The report should be in the form of a table with a count of reports against each type of problem, complaint or adverse event. Please provide both Australian figures and world-wide figures.

3. The number of implants that have been supplied and the number of revisions associated with these implants that have been reported to the sponsor and manufacturer. Please provide both Australian figures and world-wide figures.

4. Your own estimate of the revision rate for the implant – (for example: the 5 year revision rate, the 10 year revision rate, or the revision rate in number of revisions per 100 component years) and an explanation of how this revision rate was estimated.

5. Details and results of any clinical trials, clinical studies, or overseas registry information that may be available for the implant.

6. An explanation of the higher than average revision rate observed by the Australian Orthopaedic Association National Joint Replacement Register for the implant.

7. A detailed description of design changes or any other actions that may have been undertaken to improve the seemingly poor early performance of the product in relation to early revision. Please outline how the changes reduce the risk of early revision supporting your argument with clinical evidence, if available.

8. An outline of the perceived benefits of using the implant over other similar products, and how these benefits compensate for the apparently increased risk of early revision.

9. Any other information about the implant that you wish the TGA to consider in addition to the data from the AOANJRR.
# TGA’s 9 Questions

<table>
<thead>
<tr>
<th>ARTG numbers</th>
<th>Manufacturer complaint data (Tabulated Australia and Worldwide)</th>
<th>Sales data and associated revisions (Tabulated Australia and Worldwide)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Your own estimate of revision rate and explanation of how calculated.</td>
<td>Clinical and Registry data for the device</td>
<td>Your explanation for the higher revision rate in the AOANJRR data</td>
</tr>
<tr>
<td>Details of any design changes made to address revision rate</td>
<td>Outline of any benefits which outweigh risks of higher revision rate</td>
<td>Any other information</td>
</tr>
</tbody>
</table>
Could you answer these questions – **today**?

<table>
<thead>
<tr>
<th>ARTG numbers</th>
<th>Manufacturer complaint data (Tabulated Australia and Worldwide)</th>
<th>Sales data and associated failures (Tabulated Australia and Worldwide)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Your own estimate of failure rate and explanation of how calculated.</td>
<td>Clinical data for the device</td>
<td>Your explanation for the observed failure(s)</td>
</tr>
<tr>
<td>Details of any design changes made to address failure</td>
<td>Outline of any benefits which outweigh risks failure rate</td>
<td>Any other information</td>
</tr>
</tbody>
</table>
Collect Feedback

Analyse trends

What are acceptable limits?

Regular review – it’s better that you find out first

Timely responses to TGA based on your own, CURRENT data
Key elements to ensuring you get the what, when and how right.

• Provide all information requested and just the information requested
• Present the information in a logical, clear format
• Link the information – literature search and post market data
  Clinical Evidence Report → Risk Assessment → Risk mitigations
• Clinical Evidence
• Getting the numbers right
• Referencing that is organised and cross referenced in the submission
• Identify all probable and potential risks
Postmarket Tools

- Regular Reviews
- Reporting Processes
- Clinical Evidence
- Corrective and Preventive Actions
- Risk Management
- Customer Feedback
Be Prepared

It’s too late to be writing the disaster plan the day after the disaster
Postmarket for IVD’s

Sally Jennings
RA QA Affairs & IBP Manager, Abbott Diagnostics

Devices Sponsor Information Day – 15 October 2015
Death or Serious Injury

• What does this mean for an IVD?

• User – same as for a medical device
  • User – death or serious injury or potential death or serious injury

• Patient - ‘Adverse impact to patient management’
  • Patient
    • result lead to, or might have lead to, a patient management decision that resulted in death or serious deterioration in the health of the patient

Self-testing – User and Patient are the same so both criteria may apply
Potential Reportable Events for IVDs

Events which should be considered as potentially reportable:

• Death, injury or potential injury to any patient, laboratory personnel, field service engineer, or other persons
• Fire, evidence of fire, or visible smoke from a device or a device used in conjunction with another device
• Exposure or potential exposure to hazardous materials
• Adverse impact to patient management, including those caused by a delay in reporting results, including:
  • Unnecessary treatment / medication given
  • Excessive treatment / medication given
  • Insufficient treatment / medication given
  • Medication or treatment delayed or cancelled
  • Other negative impact to patient care
• Discrepant or questioned patient results, including
  • Results not consistent with clinical / patient history (including physician questioning results)
  • Different clinical interpretations of patient results
  • Questioned results from clinical studies being used for individual patient management
• Sample identification errors
• User Reports and Other Safety Issues

The manufacturer may use documented criteria for determining if there is a need to report.
Scenario 1

• Public Health
  • H1N1 pandemic
  • Government decides to use Acme Enterprises PoC test for H1N1 to screen all persons arriving in Australia by plane and boat!!
  • Doctors begin to report cases of recent travellers falling ill with H1N1

• Reportability
  • Potential for spread of H1N1 from infected people
  • Public Health threat

Timeframe for reporting – 48 hour reportable

Let’s hope it never happens!!
Scenario 2 (covered by TGA)

- **Patient impact**
  - Person with diabetes presented to emergency department in a coma and later dies
  - Patient had tested glucose levels using a self-testing glucose meter and administered insulin prior to ED admittance

- **Reportability**
  - patient death
  - Glucose meter results may have lead to an incorrect patient management decision

**Timeframe for reporting – 10 day reportable**
Scenario 3

• User impact
  • Incidents were reported by Laboratory personnel of an IVD instrument overheating and, in one case, catching fire
  • Fire was contained within instrument
  • No injury to laboratory personnel in reported cases

• Reportability
  • Potential injury (burns) to users if fire is not contained

Timeframe for reporting – 30 day reportable
Scenario 4

- Patient Impact
  - Patient sample is tested by a laboratory for creatinine and protein level
  - Creatinine reads high at 150 umol/L and the protein level read 140 g/L
  - Results are released to the treating physician who queries the creatinine result
  - No change to patient management

- Reportability
  - Potential for change to patient management if results acted on,
  BUT
  - Proteins are known to interfere with creatinine at concentrations above 100 g/L and this is clearly stated in the Instructions for Use of the creatinine assay.

Timeframe for reporting – not reportable
Questions & Discussion