Devices Sponsor Information Day

UNDERSTANDING THE TGA’S REGULATORY FRAMEWORK

SUPPORTING ORGANISATIONS —

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Clinical evidence – pre-market and post-market

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Clinical evidence
Pre-market and post-market

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Devices Sponsor Information Day 2015

15 October 2015
Outline

- Legislative basis
- Essential principles
- Clinical data
  - Clinical investigation data
  - Literature review
  - Post-market data
- Common problems
- Questions

Clinical evidence - pre-market and post-market
Legislative basis

**Therapeutic Goods Act 1989**

- Essential principles
- Medical device standards

**Therapeutic Goods (Medical Devices) Regulations 2002**

- Essential principles
- Medical devices to which the clinical evaluation procedures must be applied
- Clinical evaluation procedure

Clinical evidence - pre-market and post-market
Essential Principle 14 – Clinical Evidence

• Every medical device requires **clinical evidence**, appropriate for the use and classification of the device

• Demonstrating that the device **complies** with the applicable provisions of the **Essential Principles**

Clinical evidence - pre-market and post-market
Outline

• Legislative basis

• **Essential principles**

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• Common problems

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Clinical evidence - pre-market and post-market
## Essential Principles (EPs)

<table>
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<tr>
<th>Principle</th>
<th>EP</th>
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<td>Use of medical devices not to compromise health and safety</td>
<td>EP 1</td>
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<td>Design and construction of medical devices to conform with safety principles</td>
<td>EP 2</td>
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<td>Medical devices to be suitable for intended purpose</td>
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<td>Long-term safety</td>
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<td>Benefits of medical devices to outweigh any undesirable effects</td>
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<td>Labelling &amp; Instructions for use</td>
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Clinical evidence - pre-market and post-market
Demonstrating compliance with EPs

- Clinical evaluation procedure
  - Obtaining clinical data
  - Clinical investigation data
  - Literature review
  - Evaluation of clinical data
Demonstrating compliance with EPs – Medical Device Standards

• Compliance with applicable **medical device standards** is not required, but it is one way to establish compliance with essential principles

• The manufacturer must ensure that the clinical data obtained takes account of any **medical device standard** or conformity assessment standard that may apply to the device, e.g. ISO 5840: Cardiac valve prostheses

• If an applicable device standard is not followed, a justification would be necessary

Clinical evidence - pre-market and post-market
Outline

• Legislative basis
• Essential principles

• **Clinical data**
  – Clinical investigation data
  – Literature review
  – Post-market data
• Common problems
• Questions
Clinical investigation data

The manufacturer of a kind of medical device must obtain clinical data in relation to the device in the form of either or both of the following:

- Clinical investigation data
- A literature review

- **Full** clinical study reports demonstrating safety and/or performance in the intended use.
- Requires a written clinical expert report, with an adequate **critical** evaluation of the data.
Substantial equivalence

- Technical characteristics (e.g. materials, design, specifications, physicochemical properties, critical performance requirements, manufacturing process)
- Biological characteristics
- Clinical use
- Clinical expert should justify why each difference should not pose any impact on safety and performance.
- Non-clinical information should be included.

Clinical evidence - pre-market and post-market
Literature review

- Documentation of search and selection strategy – should be reproducible
- Adequacy of databases used
- Critical analysis and synthesis of data retrieved
- Relate these data to the intended purpose and safety profile of the device
- Include both positive and negative results
- Clinical expert should provide a critical discussion of how safety and performance of the subject device is demonstrated
- Clinical expert should discuss substantial equivalence if applicable

Clinical evidence - pre-market and post-market
Post-market data

- Particularly helpful where:
  - Paucity of clinical studies
  - Borderline clinical evidence in other respects
  - Devices where clinical studies are few or rarely conducted
  - Recertification – should provide up-to-date adverse event and complaint data for world wide sales
- Any post-market data is of use to the clinical assessor and should be provided where possible
Clinical expert

- ‘Expert’ in the relevant field
- Must be clinically qualified, commensurate with the device and its intended purpose
- Must provide critical evaluation of totality of all clinical data (and also pre-clinical data where applicable), to arrive at a reasoned conclusion on the risk-benefit profile of the device for the intended use

Critique is important: not summarising with a perfunctory conclusion. Show how the data address performance and safety

Clinical evidence - pre-market and post-market
Manufacturer’s ongoing obligations

• Maintain appropriate records:
  – Technical documentation demonstrating compliance of the device with the EPs
  – Systematically review information gained after the device was supplied in Australia, including (but not limited to):
    ▪ Literature reviews
    ▪ Device tracking and registration registers

Clinical evidence - pre-market and post-market
Outline

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Clinical evidence - pre-market and post-market
Common problems

- Absence of the required components of the clinical documentation
- Unclear intended purpose(s)
- Lack of provision of adequate information to enable an evaluator to reproduce the literature search
  - Includes lack of provision of appendices listing included and excluded articles with justification
Common problems

• Inclusion of additional papers at the end of a literature search from an unknown literature search
• All included studies are not critically analysed; there seems to be an element of ‘cherry picking’
• References to documents that have not been submitted
• Submission of any or all information that could possibly be related to this device

Clinical evidence - pre-market and post-market
Common problems

- Little or no critical assessment of the data presented:
  - No discussion of relative strengths of the data (e.g. RCTs, case control studies, case series)
  - Not establishing the validity of the data for other devices to the device under assessment (e.g. substantial equivalence)
  - Lack of discussion of the validity or otherwise of outcome measures used
Common problems

- Inappropriate selection of clinical ‘experts’
- No post-market data in cases where it is perfectly possible to supply it
Agenda

Presented by
Tamkin (Tammy) Ahmadzada, Brandwood Biomedical

Can we rely on European Evidence?

What is Clinical Evidence Anyway?

Key Messages for any device
Can we rely on European Evidence?

“In recent years the EU system has been shown to have systemic weaknesses”

- Lack of transparency about the basis of marketing approvals
- Notified bodies not assessing rigorously enough
- Level of evidence for many higher risk devices insufficient for safe widespread use.
- Less stringent assessment standards

What is Clinical Evidence Anyway?

Data + Evaluation = Evidence
Key Messages for any device

Scope

Completeness

Balance

Expertise
Define the Scope

What is the Device?

- Design, materials, variants, operation
- Sterile/non-sterile
  Single/multiple use?
- Intended use, label claims
- Contraindications
Completeness of data

- Literature
- Risk Assessment
- Clinical Investigation
- Data from Equivalent Devices
- In-House Post-Market Surveillance Data
- Public Adverse Effect Databases
Mock product: Endovascular Stent for abdominal aortic aneurysm.
Search Strategy Example

**Databases searched**
- e.g. PubMed, Google Scholar, etc.

**Search Terms**
- e.g. “Stent” AND “abdominal aortic aneurysm”
- Search filters: Review articles, studies published in the last 10 years, etc.
- Date of search

**Inclusion Criteria**
- Device application: abdominal aortic aneurysm stent (identification of equivalent devices).
- Study size: e.g. multiple patients, case reports.
- Study population: human only or animal studies?
- Follow-up period: e.g. long-term follow-up (such as five or more years).
- Article language: English
- ...

**Exclusion Criteria**
- Stents for different intended purpose or extended claims, e.g. thoracic aortic aneurysm, cerebral aneurysm.
- Applications contraindicated in the device IFU.
- ....
Completeness - **Objective** Analysis of Data

- **Existing technology and intended for an established and accepted use.**
- **Literature**
- **Post-market data**
- **Clinical Trial Data**
- **New or “unproven” technology; Extension of existing technology to a new clinical use.**

**Data on hazards and risks**
E.g. infection, rupture, leak, thrombosis, etc.

**Data on performance in clinical use**
E.g. clinical outcomes, stent deployment, removal of delivery system, etc.

**Favourable / unfavourable scientific data**
Level of Evidence
E.g. review of randomized controlled trial studies versus single case report.
Balance

Risks identified

Device Risk Assessment

- Performance Failures
- Complications
- Patient risks

- IFU
- Training
- Pre-clinical tests
- Labelling

Favourable Risk: Benefit ratio
Expertise

An individual with **clinical qualifications relevant to the device and its use**, who also has **experience in the use of the device in a clinical setting**.

- E.g. Qualified nurse for general hospital disposable equipment.
- E.g. Cardiac physician for an endovascular stent.
Key Messages for any device

Scope
Completeness
Balance
Expertise
Clinical Evidence for IVDs – Hiram Chipperfield
Background

- All opinions are my own and do not represent the views of my employer or the TGA
- Experience:

![](chart.png)

**IVDs Inclusion submissions requiring compilation of clinical evidence**
Clinical Evidence: Overall Requirements

Clinical Utility

Clinical Performance

Analytical Performance
Clinical Utility

• Usefulness of analyte or parameter in clinical decision making
• Well established analytes:
  • Stating that analyte is well established is sufficient
  • E.g. No need to summarise usefulness of hCG in pregnancy
• New analytes or new clinical uses of old analytes need evidence of clinical utility or usefulness
Analytical Performance

• Also termed “Product validation and verification”
  • Specimen type
  • Accuracy
  • Analytical sensitivity
  • Analytical specificity
  • Measuring range
  • Etc..
Clinical Performance

• The IVD's ability to correctly identify a particular clinical condition
• For well established analytes, clinical performance can be established from analytical performance
  • Comparison to approved IVD or “Gold Standard”
  • Characterised clinical specimens typically required (not just spiked specimens)
• Self-test/point of care must demonstrate clinical performance in target setting
Presentation of Clinical Evidence

• Technical File:
  • Analytical performance/performance characterisation
  • Clinical evaluation report:
    • Clinical Utility
    • Clinical Performance

• Level of Detail
  • Class 1 - Summary
  • Class 2 - Summary
  • Class 3 - Detailed
  • Class 4 - Detailed + Raw/Line data for clinical evidence
Tips

• Refer to Guidance - www.tga.gov.au
• Ensure that Manufacturer understands Australian clinical evidence requirements and can provide the necessary data
• Read the letter requesting the clinical information
• Work with manufacturers to make clinical studies easy to understand
  • Summaries of study reports can be OK
Tips

• Including published studies can significantly strengthen clinical evidence
• Some well-established products may not have clinical evidence available to current expectations
  • Identify potential gaps in clinical evidence and develop justification
  • Post-market data such as complaints rates or quality assurance (QAP) results can provide clinical evidence
Questions

Clinical evidence - pre-market and post-market