Risk Management in the Medical Device Context

Strategies to maintain device safety and performance

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Outline

• Introduction to risk management
• Why risk management is important
• What risk management should consider
• Risk management walkthrough
• Case studies

Note- information presented in this presentation is based on general, personal observations and is not binding on the TGA. You should get independent advice to ensure all of the legislative requirements are met for your matter
Let’s plan a holiday

• Where?
• Which airline?
• Which hotel?
• What activities?
• When to book by?
• What information do you need?
• What things to lock in?
• What if things go wrong?
What did we learn?

1. Risk management is part of our instinct and planning
2. We think we are good at it… and we generally are
3. There will always be gaps
4. Relies primarily on past, personal experience
5. Other’s stories and mistakes can help us!

1. Risk identification, assessment and management is a systematic and comprehensive process
2. Needs to be responsive, robust, current and effective, ‘no gaps’
3. Performed with intent, based on market information and multiple inputs and perspectives across the lifecycle of the device
Context and focus

Research and patenting

• Useful, important technology development with commercial prospect
• Understanding of clinical need and prior art
• Supported by published articles and patents by authors
• Usually about being different and being better when compared to similar technology

Regulatory and manufacturing

• Device for benefit to patients
• Understanding of clinical need, common issues and state of the art
• Supported by pre-clinical and clinical data, published literature in the field, and conformity to relevant standards
• Usually about equivalence to devices already on the market and the reduced risk or improved benefit
## Complexity adds risk

<table>
<thead>
<tr>
<th>Raw Materials</th>
<th>Critical suppliers</th>
<th>Manufacturing sites</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intended user and usability</td>
<td>Sterilisation</td>
<td>Transport/ storage/ shelf life</td>
</tr>
<tr>
<td>Standards and requirements</td>
<td>Systems, apps and data</td>
<td>Intended lifetime</td>
</tr>
</tbody>
</table>
Mindset of safety

Manufacturer
- Novelty
- Branding
- Market share
- Time to market
- Profit
- Funding

Regulator
- Novelty
- Clinical need
- Safety and quality
- Knowledge and competence
- Lifecycle monitoring
- Risk minimisation
We want the same end goal

- Safe, reliable, effective products that provides a net benefit to patients and users
- Consumers are interested and informed about their health
- Expectations that therapeutic goods are safe and effective
- Manufacturer and regulator to react quickly and appropriately in response to new risks
- The regulator balances industry and Australian public expectations
Risk management
What is risk management

- Defined in ISO 14971- systematic application of management policies, procedures and practices to the tasks of analysing, evaluating, controlling and monitoring risk
- Top management commitment- culture of safety
- The risk management process and system is an integral part of the medical device lifecycle
- A living document that captures and is updated with risks across different points of the device
  - Scope spans from design conception to patient use and disposal
  - Relevance spans from premarket approval to post-market obsolesce
- Part of the design process of a medical device
- Part of the quality management system documentation and there should be a documented procedure about who does it, how is risk determined, and how often it is reviewed
What this tells the TGA

- Good risk assessment documentation and processes:
  - Demonstrates that the manufacturer is aware of risks and hazards associated with the device
  - Demonstrates that the manufacturer has taken steps to mitigate risk
  - Demonstrates that design inputs are validated and linked to risk management
  - Demonstrates that the outputs have been verified and acceptable
  - Demonstrates that the residual risk is acceptable
  - Demonstrates the manufacturer has responded appropriately to new or existing hazards or risks
  - Demonstrates that they can be a responsible and competent manufacturer
Main standards

INTERNATIONAL STANDARD

ISO 13485
Third edition
2016-03-01

Medical devices — Quality management systems — Requirements for regulatory purposes

INTERNATIONAL STANDARD

ISO 14971
Second edition
2007-03-01

Medical devices — Application of risk management to medical devices

Dispositifs médicaux — Application de la gestion des risques aux dispositifs médicaux
Relevant Australian requirements

- All devices have to comply with Essential Principles (EPs)- Schedule 1 of Therapeutic Goods (Medical Devices) Regulations 2002
- Of particular relevance when considering risk are EP 1, 2 and 6.
- This also include compliance with conformity assessment procedures which demonstrate manufacturer control and review of processes
- International regulators may have their own specific requirements

EP1- Use of medical devices not to compromise health and safety
EP2- Design and construction of medical devices to conform with safety principles
EP6- Benefits of medical devices to outweigh any undesirable effects
Essential Principle 2

2 Design and construction of medical devices to conform with safety principles

(1) The solutions adopted by the manufacturer for the design and construction of a medical device must conform with safety principles, having regard to the generally acknowledged state of the art.

(2) Without limiting subclause (1), in selecting appropriate solutions for the design and construction of a medical device so as to minimise any risks associated with the use of the device, the manufacturer must:

   (a) first, identify hazards and associated risks arising from the use of the device for its intended purpose, and foreseeable misuse* of the device; and

   (b) second, eliminate, or reduce, these risks as far as possible by adopting a policy of inherently safe design and construction; and

   (c) third, if appropriate, ensure that adequate protection measures are taken, including alarms if necessary, in relation to any risks that cannot be eliminated; and

   (d) fourth, inform users of any residual risks that may arise due to any shortcomings of the protection measures adopted.

*Note: misuse includes incorrect or improper use of the device
Is ALARP enough?

- In most risk management processes, some risk can be controlled to ‘as low as reasonably practicable’ (ALARP)
- This wording is not used in Australian legislation for medical devices
- We expect the risk to be minimised, or eliminated as far as possible
- There are issues where a manufacturer does not want to take certain measures based on cost
- There is inherent risk in any device or medical procedure, but cost is not an acceptable justification for lack of risk minimisation if the risk to patient can be reduced
- What is the human cost?
- Some of the benefits of taking on the risk must flow to the patient also
FMEA

• Failure mode and effect analysis (FMEA) is a popular structured approach to identify possible failures through the different stages of device design, manufacture, assembly, transport and use
• Detailed process and examples- IEC 60812
• Often adopted by device manufacturers as their risk assessment process
• May be split into design (dFMEA), process (pFMEA) and user (uFMEA) sub documents.
• There are other risk management approaches that are valid

Potential issues
• Although it emphasises on failures, risks and hazards that may not fit the definition of ‘failure’ should also be captured for it to meet ISO 14971 requirements
• A failure can have multiple root causes- each of the root causes should be identified, assessed and controlled separately
The Swiss cheese model of failures
Identifying risks and hazards

**Hazard**- source of harm

**Risk**- combination of probability of occurrence of harm and severity of that harm

- Input by diverse panel of experts- management, manufacturing, process, engineers, clinical expertise, users, quality
- Risk for the device and kind of device- what news or literature risks have been reported? Recalls from competitors? New trends or complications? Clinical reports and near misses?
- What requirements are listed in applicable standards? E.g. if it is an active device or has software- IEC 60601. If implantable- ISO 14630 or ISO 14708
- Should be specific events and root causes to cover scenarios. Not ‘bad material’ or ‘material failure due to inadequate properties’ but e.g. ‘fatigue fracture due to early failure of component x’
Risk assessment

ISO 14971 only provides an example. It is up to the manufacturer to design their severity and probability levels and some include additional considerations (e.g. detectability).

- Categories should be clearly defined to minimise confusion or ambiguity
- Probabilities should be quantified
- Thresholds should be appropriate and reasonable
- Standards set the minimum requirements
## Risk acceptability matrix

<table>
<thead>
<tr>
<th>Probability</th>
<th>S1 Negligible</th>
<th>S2 Minor</th>
<th>S3 Serious</th>
<th>S4 Critical</th>
<th>S5 Catastrophic</th>
</tr>
</thead>
<tbody>
<tr>
<td>P5 Frequent</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P4 Probable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P3 Occasional</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P2 Remote</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P1 improbable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Consider probability based on literature, similar devices and post-market information

- **Acceptable risk**
- **Acceptable with review**
- **Unacceptable Risk**
## Problematic acceptability matrix

<table>
<thead>
<tr>
<th>Probability</th>
<th>S1 Negligible</th>
<th>S2 Minor</th>
<th>S3 Serious</th>
<th>S4 Critical</th>
<th>S5 Catastrophic</th>
</tr>
</thead>
<tbody>
<tr>
<td>P5 Frequent (&gt;5%)</td>
<td>?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P4 Probable (0.25-5%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P3 Occasional (0.025-0.25%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P2 Remote (0.001-0.025%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P1 improbable (&lt;0.001%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **Acceptable risk**
- **Unacceptable Risk**
Risk mitigation

• Top management commitment
• Elimination by design is preferred option- can the risk be designed out by eliminating certain materials, or design features, or compatibility
  – E.g. gas tubing threading- cannot physically connect the wrong kind of tubing/ gas
  – Material incompatibility e.g. ECC from acrylics and alcohol- almost impossible to avoid alcohols in hospital setting
• Early intervention and design is cheaper and more effective than late in process
• Mitigation may mean doing bench tests to specify acceptable limits- e.g. for a bone cement- meeting fatigue, creep, tensile, flexure modulus requirements from e.g. ISO standard
• Administration controls- decide how often process is monitored
Residual risk

• Consider the risk carefully after evaluation
• Is there still a residual risk?
• Do risk control measures introduce new hazards or affect other hazards?
• Some risks are known complications and can’t be avoided
  – Pass on information to user and patient in instructions for use or patient information leaflet
• Perform an overall risk/benefit analysis if medical benefits of intended use outweigh the residual risk
• Healthcare professionals also have a responsibility to discuss and inform patients of risk associated with device and procedure
Example from IEC 60812, RPN- risk priority number (severity x probability)

<table>
<thead>
<tr>
<th>Subsystem</th>
<th>Assembly</th>
<th>Component</th>
<th>Local effect</th>
<th>Final effect</th>
<th>SEV</th>
<th>CLASS</th>
<th>Potential cause(s)/ mechanism(s) of failure</th>
<th>Ocurr</th>
<th>Current design controls prevention</th>
<th>Current design controls detection</th>
<th>RPN</th>
<th>Recommended action(s)</th>
<th>Responsibility and target completion date</th>
<th>Action results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Power supply</td>
<td></td>
<td>V1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Battery voltage + shorts to ground</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D1</td>
<td>Short</td>
<td>Battery failure</td>
<td>Battery voltage + shorts to ground</td>
<td>Battery failure</td>
<td>10</td>
<td></td>
<td>Material breakdown</td>
<td></td>
<td>Selection of higher quality and rating</td>
<td>Evaluation and reliability verification testing</td>
<td>30</td>
<td>action</td>
<td></td>
<td></td>
</tr>
<tr>
<td>D1</td>
<td>Open</td>
<td>No reverse voltage protection</td>
<td>No reverse voltage protection</td>
<td>No reverse voltage protection</td>
<td>2</td>
<td></td>
<td>Inherent defect of the component</td>
<td></td>
<td>Selection of higher quality and rating</td>
<td>Evaluation and reliability verification testing</td>
<td>12</td>
<td>action</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C9</td>
<td>Short</td>
<td>Battery failure</td>
<td>Battery failure</td>
<td>Battery failure</td>
<td>10</td>
<td></td>
<td>Dielectric breakdown</td>
<td></td>
<td>Selection of higher quality and rating</td>
<td>Evaluation and reliability verification testing</td>
<td>30</td>
<td>action</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C9</td>
<td>Open</td>
<td>No EMI filtering</td>
<td>No EMI filtering</td>
<td>No EMI filtering</td>
<td>2</td>
<td></td>
<td>Inherent defect of the component</td>
<td></td>
<td>Selection of higher quality and rating</td>
<td>Evaluation and reliability verification testing</td>
<td>4</td>
<td>action</td>
<td></td>
<td></td>
</tr>
<tr>
<td>L1</td>
<td>Open</td>
<td>No V1–</td>
<td>No V1–</td>
<td>No V1–</td>
<td>9</td>
<td></td>
<td>Inherent defect of the component</td>
<td></td>
<td>Selection of higher quality and rating</td>
<td>Evaluation and reliability verification testing</td>
<td>18</td>
<td>action</td>
<td></td>
<td></td>
</tr>
<tr>
<td>R01</td>
<td>Open</td>
<td>No voltage for the item switching circuit</td>
<td>No voltage for the item switching circuit</td>
<td>No voltage for the item switching circuit</td>
<td>9</td>
<td></td>
<td>Bonding or material crack</td>
<td></td>
<td>Selection of higher quality and rating</td>
<td>Evaluation and reliability verification testing</td>
<td>18</td>
<td>action</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Figure B.1 – FMEA for a part of automotive electronics with RPN calculation
Post-production monitoring

Manufacturers are responsible for **actively** monitoring risks of their devices on the market, not just when things go wrong, or wait for things to go wrong

- Notify the TGA
- Identify new hazards and update risk management documentation (use other manufacturer’s issues and cases as inputs too)
- Update risk probability/ severities
- Perform CAPA investigation and root cause analysis
- Consider new or additional mitigation measures
  - E.g. new product version design
  - Add new features e.g. alarms
  - Closer monitoring or alter acceptability criteria
    - This changes product specifications and should be re-validated
  - Undertake appropriate recall action
Symptom of issues

- Observable issues from our premarket assessments and post-market investigations:
  - Hazard/ risk not identified or updated/ acknowledged
  - Risk matrix not appropriate
  - Risk not properly mitigated
  - Inconsistency between risk document and other documents
  - Tests and validations not carried out per risk management documents
  - Risk not informed by post-market experience
  - No regular review or update

- Issue with Risk management process and documents points to non-compliance with Essential Principle 2
  - Grounds for TGA to reject new device application or to cancel the ARTG entry of existing device
Key ideas

• The responsibility of demonstrating Conformity (i.e. undertaking Conformity Assessment Procedures) is the responsibility of the MANUFACTURER

• The main role of the National Regulatory Authority is to MONITOR and ASSESS product and manufacturer compliance. Whether pre or post-market based the regulatory strategies rely on sampling (the Market, Products, the QMS, the Design Dossier…)

• National Regulatory Authorities receive and investigate adverse event reports not only to ensure Performance and Safety BUT ALSO to monitor the performance, suitability of the manufacturer’s QMS and its responsiveness to post market issues.
Take home message

• Risk management process is a very important part of maintaining long term device safety and meeting regulatory requirements for any medical device manufacturer
• Consider all hazards and risks methodically for intended use and foreseeable misuse or incorrect use
• Risks must be controlled/ mitigated to an acceptable level
• The risk assessment documentation must be reviewed regularly and periodically and kept up to date

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