Comments from BSI – Notified Body

1. The Essential Principles (TG(MD)R 2002)), Essential Requirements (93/42/EEC) Safety and Performance Requirements (draft MDR) have similar requirements:
   - Safe
   - Perform as intended
   - Benefits>risks
   - Lifetime
   - …
   - Information supplied

There are small changes in wording that could change interpretation, however in general the big concepts are similar.

2. Leaving dates on standards, will date the guidance quickly. If dates are removed, users could refer to the latest version:
   - ISO14155:2011 on Good Clinical Practice.
   - ISO14971:2007 Application of risk management to medical devices
   - ISO 11979-7:2006 on intraocular lenses
   - ISO 5840:2005 on cardiac valve prostheses

ISO 13485:2016 was published in March 2016, ISO 14155 and ISO 14971 are currently under review.

3. Definitions

<table>
<thead>
<tr>
<th>MedDev 2.7.1 Rev 3:</th>
<th>MedDev 2.7.1 Draft Rev 4:</th>
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<tbody>
<tr>
<td>• Adverse Event</td>
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<tr>
<td>• Clinical Data</td>
<td>• Bias</td>
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<td>• Clinical Evaluation</td>
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<td>• Clinical Evidence</td>
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<td>• Clinical Investigation</td>
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<td>• Clinical Investigation Plan</td>
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<td>• Clinical Investigator</td>
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<td>• Clinical Performance</td>
<td>• Clinical Performance</td>
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<td>• Clinical Safety</td>
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<td>• Conformity Assessment</td>
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<td>• Serious Adverse Event</td>
<td>• Clinical Use</td>
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<td>• Harmonised Standards</td>
<td>• Equivalent Device</td>
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<td>• Technical Documentation</td>
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<td>• Harmonised Standards</td>
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<td>• Hazard</td>
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<td>• Hazard due to substances and technologies</td>
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<td>• Incident</td>
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<td>• Information materials supplied by the manufacturer</td>
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<td>• Intended purpose</td>
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<td>• PMCF Plan</td>
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<td>• Risk</td>
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<td>• Serious Adverse Event</td>
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<td>• Sufficient Clinical Evidence</td>
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</tbody>
</table>
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Draft MDR (subset):
- Clinical evaluation
- Clinical investigation
- Investigational device
- Clinical investigation plan
- Clinical data
- Sponsor
- Subject
- Clinical evidence
- Clinical performance
- Clinical benefit
- Investigator
- Informed consent
- Ethics committee
- Adverse event
- Serious adverse event
- Device deficiency
- Post market surveillance
- Market surveillance
- Recall
- Withdrawal
- Incident
- Serious incident
- Serious public health threat
- Corrective action
- Field safety corrective action
- Field safety notice
- Harmonised standard
- Common specification

EN ISO 14155:2011:
- Adverse device effect
- Adverse event
- Audit
- Blinding/masking
- Case report forms
- Clinical investigation
- Clinical investigation plan
- Clinical investigation report
- Clinical performance
- Comparator
- Contract research organisation
- Coordinating investigator
- Data monitoring committee
- Deviation
- Device deficiency
- Endpoint(s)
- Ethics committee
- Hypothesis
- Independent
- Informed consent process
- Investigation site
- Investigational medical device
- Investigator
- Investigators brochure
- Legally authorised representative
- Malfunction
- Medical device
- Monitoring
- Multicentre investigation
- Objective
- Points of enrolment
- Principal investigator
- Randomisation
- Recruitment
- Serious adverse device effect
- Serious adverse event
- Source data
- Source document
- Sponsor
- Subject
- Unanticipated serious adverse device effect
- Use error
- Vulnerable subject

There are small changes in wording (i.e. addition of ‘human’, addition of ‘sufficient’) that could change interpretation, however many of the big concepts (i.e. clinical safety, clinical performance) are similar.

The draft MDR and draft MedDev 2.7.1 biggest differences to TGA draft guidance:

- Only allow one equivalent device
- Literature included only from peer-reviewed publications
- Not allowing inclusion of expert opinion

New concepts in TGA draft document (i.e. predicate, similar marketed device, direct clinical evidence, indirect clinical evidence) are clear.

Comments as of May 2016
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Is the definition of ‘substantial equivalence’ intended to be the same as the US FDA?
Is the intention that ‘effectiveness’ and ‘clinical performance’ are synonyms?

4. Requirements for the Clinical Evaluation Report between draft MedDev 2.7.1 and TGA draft guidance:
   a. Device description, lineage and version if applicable
   b. Intended purpose/indications and claims
   c. Regulatory status in other countries
   d. Summary of any relevant pre-clinical data
   e. Demonstration of substantial equivalence (if applicable)
   f. Overview of clinical data
   g. Critical evaluation of clinical data
   h. Critical evaluation of post-market data (clinical experience)
   i. Risk analysis and risk management
   j. Instructions for use, labelling and other documents supplied with the device
   k. Risk-benefit analysis
   l. Conclusions
   m. The name, signature and curriculum vitae of the clinical expert and date of report

Reports generated for compliance in the EU could also meet requirements for Australia. Requirements limiting the number of equivalent devices and restricting literature to peer-reviewed may mean that a report generated for Australia may need to be re-written for the EU.

5. Definition of ‘Equivalence’ and requirement for ‘no clinically significant difference’ draft MedDev 2.7.1 and TGA draft guidance are similar:
   • Clinical – when used for same clinical condition or purpose, same site in body, similar population including age, anatomy, physiology and similar clinical performance of device, deployment methods
   • Technical – materials, design, function, energy source etc.
   • Biological – biocompatibility

Draft MDR and draft MedDev 2.7.1 Rev 4 have more details, however the interpretation of equivalence is similar.

6. The addition of Risk:Benefit to draft TGA guidance is similar to draft MedDev 2.7.1 Rev 4.
   a. The strengths and limitations of the clinical data presented in support of the safety and performance of the device for the intended purpose (e.g. level of evidence, bias, confounders, length of follow-up).
   b. The clinical significance of the benefits of the device for the intended purpose(s) as demonstrated by the clinical data.
   c. The probability of patients receiving the benefits of the device.
   d. The duration of the proposed benefits of the device.
   e. The safety issues identified in the clinical investigation data and/or literature review and post-market data (clinical experience) for the intended purpose, as well as theoretical risks associated with the clinical use of the device that the data may not have captured e.g. misinterpretation or misuse of the device.
   f. The probability of patients experiencing an adverse event from the device.
   g. The duration and severity of adverse events caused by the device.
   h. Whether there are mitigation strategies that have been implemented to address real or theoretical safety issues i.e. risk management documentation and IFU/labelling.
   i. Any issues of uncertainty surrounding the application of the device for its intended purpose, e.g. limitations in the statistical analysis, generalizability of results to an Australian population.

Both Australian and EU guidance is similar to US FDA Guidance 1772 (2012). FDA benefits (Type, Magnitude, Probability of patient experiencing one or more benefits, Duration of effects). FDA risks (Severity, Type, Number / Rate, Device related – serious, non-serious, Procedure related, Probability of harmful event, Duration of harmful event, Risk of false positive / false negative). This is an improvement for Australian guidance, EU guidance and EN ISO 14971.

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7. Requirements for Conclusions:
   a. Clinical information on predicate/similar marketed device demonstrated to be substantially equivalent which is supportive of the safety and performance of the device
   b. Clinical evidence demonstrates benefit
   c. The device performs as intended
   d. Post-market data shows a low and acceptable level of adverse events
   e. The residual risks have been mitigated with appropriate justification, for example, inclusion of relevant statements in the IFU documentation
   f. The benefits outweigh the risks of the device

Draft MedDev 2.7.1 has similar requirements for draft TGA guidance. EU requirements include documented justification for no clinical investigation and documented justification for no post-market clinical follow-up if applicable.

8. The requirements for who can conduct a clinical evaluation – competent clinical expert:
   • A ‘competent clinical expert’, usually someone with experience in the use of the device type in a clinical setting and relevant clinical qualifications, must evaluate all the clinical data and sign the clinical evaluation report.
   • For example, for a coronary stent submission the clinical expert should be a practising interventional cardiologist. In order for the clinical assessor to determine whether an appropriate clinical expert has been chosen, the full curriculum vitae of the clinical expert who evaluates the clinical data and signs the clinical evaluation report should be included in the CER. Any convergence of interests or potential for conflict with the sponsor or manufacturer must be acknowledged and addressed.

Draft MedDev 2.7.1 Rev 4 requirements are more prescriptive:
   • Possess knowledge of the following:
     - research methodology (including clinical investigation design and biostatistics);
     - information management (e.g. scientific background or librarianship qualification; experience with relevant databases such as Embase and Medline);
     - regulatory requirements; and
     - medical writing (e.g. post-graduate experience in a relevant science or in medicine; training and experience in medical writing, systematic review and clinical data appraisal).
   • With respect to the particular device under evaluation, the evaluators should in addition have knowledge of:
     - the device technology and its application;
     - diagnosis and management of the conditions intended to be diagnosed or managed by the device, knowledge of medical alternatives, treatment standards and technology (e.g. specialist clinical expertise in the relevant medical specialty).
   • The evaluators should have at least the following training and experience in the relevant field:
     - a degree from higher education in the respective field and 5 years of documented professional experience; or
     - 10 years of documented professional experience if a degree is not a prerequisite for a given task.

9. Specific high risk devices section is not covered in any other regulatory guidance.
   • Total and partial joint prostheses
   • Cardiovascular devices to promote patency or functional flow (stents, implants for abdominal aortic aneurysm repair, implants for patent ductus arteriosus repair, IVC filters)
   • Electrical impulse generators
   • Heart valve replacements using a prosthetic valve
   • Supportive Devices - Meshes, Patches and Tissue Adhesives
   • Demonstrating the safety of implantable medical devices (AIMDs) in the magnetic resonance environment

Suggestions for dependent variables, sample sizes and duration of follow-up are very useful. There are suggestions that the EU will develop Common Specifications with similar details. Hopefully the EU will consider guidance already developed by other regulatory authorities.

Comments as of May 2016