Leveraging Regulatory Controls for Product Development
Points to Cover

✓ Creating the right Culture
✓ Design Controls and V&Vs
✓ Pre-Clinical Testing
✓ Clinical Testing
✓ Conclusion
Creating the right culture
What to look for in hiring regulatory expertise?
Design Controls & V&Vs
The Product Development Lifecycle

**FDA Guidance: Design Verification & Validation (V&Vs)**

Design Controls

ISO 13485 Clause 7.4

21 CFR 820.30

US Classification & Regulation

**Class I**
- General Controls: GMP, Labelling etc.
- No premarket review

**Class II**
- Special Controls: Device specific guidances and standards
- Premarket Notification and 510(k) clearance

**Class III**
- Full Safety and Efficacy review including clinical data
- Premarket Approval (PMA)
Device Development

- Risk Analysis (ISO 14971)
  - Do it Early and Often!
- Design Validation & Verification
  - Testing
  - Clinical Trials
- Final Design
- Manufacturing Quality System
- Regulatory Submission

Prototype
Pre-Clinical Testing
Safety Evaluation Outline

Device Definition
- Intended use
- Indications for use
- Instructions for use
- Principles of operation
- Extent of use
- Device categorisation

Physical Characterisation

Chemical Characterisation

Toxicological Risk Assessment

Biological Data

Interpretation of Biological Data

Overall Biological Risk Assessment & Evaluation
Toxicological Risk Assessment

Chemical Characterisation

Toxicological Risk Assessment

Contract Research Organisation

Severity of harm

Likelihood

<table>
<thead>
<tr>
<th>Severity</th>
<th>Unlikely</th>
<th>Plausible</th>
<th>Likely</th>
<th>Very Likely</th>
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<tbody>
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<td>Insignificant</td>
<td>Trivial</td>
<td>Trivial</td>
<td>Low</td>
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<tr>
<td>Slight</td>
<td>Trivial</td>
<td>Low</td>
<td>Low</td>
<td>Medium</td>
</tr>
<tr>
<td>Moderate</td>
<td>Low</td>
<td>Low</td>
<td>Medium</td>
<td>High</td>
</tr>
<tr>
<td>Severe</td>
<td>Medium</td>
<td>Medium</td>
<td>High</td>
<td>Very High</td>
</tr>
<tr>
<td>Very Severe</td>
<td>Medium</td>
<td>High</td>
<td>Very High</td>
<td>Very High</td>
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Safety Evaluation
✓ Don’t just “test” for it
✓ Use all the existing data, to reduce testing

Risk Management
✓ Evaluation and Testing is done in a “risk management process.”
✓ Very specialised skill
✓ Ongoing, non-static
Clinical Evidence
What is Clinical Evidence?

Data + Evaluation = Evidence
The Literature Search

Databases searched
- e.g. PubMed, Google Scholar, emBase, Cochrane etc.

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

Inclusion Criteria
- Application: abdominal aortic aneurysm stent
- Study size: e.g. multiple patients, case reports.
- Study population: human only or animal studies?
- Follow-up period

Exclusion Criteria
- Stents for different intended purpose or extended claims, e.g. thoracic aortic aneurysm, cerebral aneurysm.
- Applications contraindicated in the device IFU. ....
Post-Market Data

Adverse event databases

- Database of Adverse Events Notifications (DAEN):
  - DAEN – medicines: provides information about adverse events related to medicines and vaccines used in Australia.
  - DAEN – medical devices: provides information about adverse events related to medical devices used in Australia.
- System for Australian Recall Actions (SARA):
  - Provides information about recall actions occurring in Australia for therapeutic goods. The Database holds information on recall actions that have been undertaken in Australia since 1 July 2012.

In-house complaints data

Reports of clinical experience
MAufacturer and User Facility Device Experience Database - (MAUDE)

80,000 to 120,000 reports EACH YEAR

www.fda.gov/cdrh/maude
Objective Analysis of Data

**Existing technology and intended for an established and accepted use.**

**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.
- Some of this may be pre-clinical

**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 and a favourable risk : benefit ratio

- Risks identified
  - Performance Failures
  - Complications
  - Patient risks

- Risk Mitigations and Clinical Benefits
  - Training
  - Pre-clinical tests
  - Labelling
  - Therapy/Diagnosis
Who needs clinical a trial?

<table>
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<tr>
<th>Submission Type</th>
<th>Requirement</th>
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<tbody>
<tr>
<td>Premarket approval (PMA)</td>
<td>Always requires direct clinical trial data (may be submitted in modules</td>
</tr>
<tr>
<td></td>
<td>–with preclinical data under review pending completion of clinical trials)</td>
</tr>
<tr>
<td>Humanitarian device exemption</td>
<td>Possibly – but only to support safety</td>
</tr>
<tr>
<td>510(k)</td>
<td>Clinical data in ~15% of cases</td>
</tr>
<tr>
<td>De novo 510(k)</td>
<td>Almost always</td>
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</table>
So which 15%?

- New clinical indications not present in predicates
- Substantially new technology
- All de novo submissions
- If in doubt – preconsult
  - Pre-Submit and Meetings with FDA Staff
Alternatives to Clinical Trials?

Registries
Collections of electronic health records
Healthcare claims databases
...
Who Does the Clinical Evaluation? Individual or Team?

• Qualifications
  • Degree + 5 years experience
  • 10 years experience alone

• Knowledge
  • the Device and its application
  • Specialist Clinical Expertise
  • Research methods, (including statistics)
  • Regulatory Requirements
  • Medical Writing (including practices of systematic review)

MEDDEV 2.7.1/4 Section 6.4
Conclusion
Key Points

• Regulatory requirements are the result of a consensus of best practices

• The conservative check-the-box approach can hamper innovation

• Risk Based Management of the development process can create significant savings

• Maintain a global perspective
Leveraging Regulatory Controls for Product Development

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