Device Development and Design Control

European, US and International Medical Device Standards and Regulations Orally, Inhaled and Nasal Drug Products

“Doing the Right Thing” in the Changing Culture of Design and Development of Inhalation and Nasal Drug Products: Science, Quality, and Patient-Focus

Premise:
Medical Devices are often more technically complicated than Medicines and yet as a Rule are less prescriptively regulated
[Principle of Proportionality versus the Precautionary Principle]

Topics:
- Device-Regulation and the Drug-Device Borderline
- “Combination” Products
- Design and Risk Management
- Postmarket Surveillance

Small Print
The views expressed are those of the presenters and are not necessarily the views of our respective Companies or of the IPAC-RS Membership
Device Development and Design Control

Device Characteristics, eg:

**Intended Use**
- Indications, purpose
- Patient characterisation
- Sequence of operation
- Reliability
- Environment
- Contraindications
- Disposal

**Intended Contact**
- Biological compatibility
- Duration, longevity
- Bioactivity
- Bioabsorbance

**Materials of Construction**
- Properties of materials
- Physical compatibility
- Structural integrity
- Packaging materials
- Cleaning, disinfection, sterilisation
- Environmental compatibility

**Intended User**
- Physician, nurse, porter, auxiliary, patient
- Ergonomics, dexterity, handling training, age, disability, intellectual acumen
- Necessary accessories
- Installer, biomedical engineering (acceptance testing)
- Service and maintenance

**Device Characteristics, eg:**

**Energy / Substances**
- Delivery or extraction
- Quality, quantity
- Control and duration
- Justification, optimisation and dose

USA Medical Device Regulations

**Statutory Authorities:**

- Federal Food, Drug, Cosmetic Act (FD&C Act)
- Medical Device Amendments of 1976 (MDA)
- Safe Medical Devices Act of 1990 (SMDA)
- [Medical Devices Amendments of 1992]
- [FDA Export Reform and Enhancement Act of 1996]
- FDA Modernization Act of 1997 (FDAMA)
- Medical Device User Fee and Modernization Act 2002 (MDUFMA)
USA Medical Device Regulations

Pre-Amendments

- Class I
- Class II
- Class III

Post-Amendments

- Substantially Equivalent
  - Premarket Notification (510K)
  - Call for PMA ($513)
  - Access to Market

- Not Substantially Equivalent
  - PMA or PDP

Provisions for:
- exemptions from Premarket Notification
- reclassification
- PMAs for Pre-Amendments Class III devices

PMA = Pre-Market Authorisation
PDP = Product Development Protocol

European Regulations

Directives:

- 90/385/EEC Active Implantable Medical Devices
- 93/42/EEC Medical Devices
- 98/79/EC In Vitro Diagnostic Medical Devices
- 2000/70/EC Devices Incorporating Human Blood Derivatives
- 2003/12/EC Reclassification of Breast Implants
- 2003/32/EC Tissues of Animal Origin
- 2004/23/EC Human Tissues and Cells
- 2005/50/EC Reclassification of total joint replacements
- 2007/47/EC Revision of MD, AIMD and Biocidals Directives

and, other Directives which impact on Medical Devices
Medical Device Directive 93/42/EEC

The PLAYERS:

- **Manufacturer**
  - Registrations
  - Surveillance
  - Vigilance
  - Enforcement
  
  ![EC Symbol](CE)

- **Notified Body**
  - Liaise other NB’s
  - NB-MED

- **Competent Authority**
  - Liaise other CA’s
  - EC Commission
  - MSOG, NBOG

- **Inspection**
  - “Certification”

- **Accreditation**
- **Consultation**
- **Surveillance**
- **Enforcement**

- **Conformity Assessment** (MDD Annexes II-VII)

- **CE MARKING**

- **Technical Dossier**
  - **In vitro Tests**
  - **In vivo Tests**

- **Clinical Evaluation**

- **Determine Conformity**

- **Conformity Assessment**

- **National MDD Transpositions**
  - 30 EEA Member States + Switzerland
  - Labelling
  - Registration

- **Intended Purpose**

- **Essential Requirements**

- **Analyse Device**

- **Classify Devices**
  - CLASS I
  - CLASS IIa
  - CLASS IIb
  - CLASS III
USA Combination Products

Determining Legal Status

Must take into account **Primary Mode of Action** (PMOA)

**“Primary mode of action”** defined as “the single mode of action of a combination product that provides the most important therapeutic action of the combination product.”

Must take into account statutory and regulatory definitions

- Biologic → CBER
- Device → CDRH
- Drug → CDER

Must take into account FDA precedents [….or take advantage of a myriad of FDA decisions]

If unsure of PMOA can apply to Office of Combination Products for determination of lead FDA Centre

---

EU Combination Products

Determining legal status

**Medical Device** does *not* achieve its **principal intended action** in or on the human body by pharmacological, immunological or metabolic means but which may be assisted in its function by such means

Drug - Device Combinations *(MDD Article 1.3)*
- if intended for administration of drug then medical device (e.g. empty syringe)
- unless drug and device are presented as integral non-reusable product then regulated as a drug (e.g. pMDI or pre-filled syringe)
  - relevant Essential Requirements of Annex I of MDD apply as far as safety and performance related device features are concerned

Drug vs Device Demarcation *(MDD Article 1.4)*
- if action of drug is only ancillary then combination is a Medical Device,
  - drug aspect must be verified by analogy to methods in ICH
  - Notified Body must seek scientific opinion of Competent Authority (drugs)

From 2010 the test of **principal mode of action** will also apply *(MDD Article 1.5)*
### Combination Products

#### Examples:

- **Drug Eluting Stent**
  - Primary Mode of Action:
    - Stent maintains patency of artery
  - Secondary Action:
    - Drug reduces inflammation and restenosis of artery

- **Drug Eluting Disk**
  - Primary Mode of Action:
    - Chemotherapy for brain tumor
  - Secondary Action:
    - Localised drug delivery

---

#### Combination Products

**Examples:**

- pMDI
  - Nebulizer
- pMDI with Expansion Chamber
  - Co-packaging
**Medical Device Regulations**

**Summary Comparison:**

<table>
<thead>
<tr>
<th>Regulator (enforcement)</th>
<th>Authorisation</th>
<th>Definitions, Classification</th>
<th>General Requirement</th>
<th>Specific Criteria</th>
<th>Conformity Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>CA's</td>
<td>NB's</td>
<td>=</td>
<td>=</td>
<td>=</td>
<td></td>
</tr>
<tr>
<td>FDA</td>
<td>FDA Centre</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prefecture</td>
<td>MHLW</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Emphasis**

<table>
<thead>
<tr>
<th>Self-regulation</th>
<th>STDK, PMA</th>
<th>Notification and Licensing</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Full Quality System (design and production)**

<table>
<thead>
<tr>
<th>Optional (but not available for Class I)</th>
<th>Mandatory Class II-III (some Class I)</th>
<th>Mandatory (EO excludes most Class I)</th>
</tr>
</thead>
</table>

---

**ICH Q-Documents (Drugs)**

<table>
<thead>
<tr>
<th>Q1</th>
<th>Stability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q2</td>
<td>Analytical Validation</td>
</tr>
<tr>
<td>Q3</td>
<td>Impurities</td>
</tr>
<tr>
<td>Q4</td>
<td>Pharmacopoeias</td>
</tr>
<tr>
<td>Q5</td>
<td>Quality of Biotech Products</td>
</tr>
<tr>
<td>Q6</td>
<td>Specifications</td>
</tr>
<tr>
<td>Q7</td>
<td>Good Manufacturing Practice</td>
</tr>
<tr>
<td>Q8</td>
<td>Pharmaceutical Development</td>
</tr>
<tr>
<td>Q9</td>
<td>Quality Risk Management</td>
</tr>
<tr>
<td>Q10</td>
<td>Pharmaceutical Quality Systems</td>
</tr>
</tbody>
</table>

**GHTF & ISO/IEC (Devices)**

| SG 1 | Essential Principles  |
| SG2  | Vigilance and PMS    |
| SG3  | Quality Systems       |
| SG4  | Quality System Auditing Practices  |
| SG5  | Clinical Safety and Performance  |

| ISO 14971 Risk Management  |
| ISO 13485 Quality Management  |
Design and Risk Management

Risk analysis
- Intended use/intended purpose identification
- Hazard identification
- Risk estimation

Risk evaluation
- Risk acceptability decisions

Risk control
- Option analysis
- Implementation
- Residual risk evaluation
- Overall risk acceptance

Post-production information
- Post-production experience
- Review of risk management experience

ISO 14971

Design and Risk Management

Market Requirements
- Pre-Marketing Requirements:
  - User requirements
  - Market Analysis
  - Reimbursement Analysis
  - Purchaser requirements
  - Post Marketing Requirements

- Post-Marketing Requirements:
  - Health Technology Assessment
  - Economic Dossier
  - Campaigns
  - Training/verification
  - Clinical Guidelines

Technical Requirements
- Design:
  - User Requirements Specifications
  - Detailed Requirement Specifications
  - Risk Management
  - Clinical Evaluation
  - Essential Requirements
  - Verification and validation
  - Design Transfer

- Production:
  - Purchase materials
  - Processing
  - Final test and inspection

- Distribution:
  - Training
  - Traceability/tracking
  - Service and maintenance

Quality Management System
- Design Control
- Production Control
- Post-Marketing Surveillance

- Early warning of problems
  - Interventional study
  - Observational study
  - Complaints
  - Field service reports
  - Training
  - Medical Devices Vigilance
  - User feedback
  - Scientific literature
  - Clinical guidelines
  - Standards development
  - Design evolution
  - Off-label use

ICH Q9
**Design Improvement – Drug Product**

Change to Plastic used in Inhalation Device (e.g. valve within a pMDI)

- Complete process can take approx. 3 – 5 years
- Extremely resource intensive

**Design Improvement – Medical Device**

Change to Plastic used in Inhalation Device (e.g. refillable nebulizer)

- Change implemented in a few months
- Assumes device company is accredited to ISO 13485
*Post-Market Surveillance*

Customer Satisfaction \(\rightarrow\) Continuous Improvement

---

**PMS**

**CAPA**

**MDV**

**MDR**

Public Health Protection

---

*Post-Market Surveillance*

**Feedback (Life-Cycle)**

**Considerations, eg:**

- Design Evolution
- Incident or Near Incident
- Corrective Action Recall
- New Scientific Knowledge
- User Inspiration

Each of the above should prompt re-evaluation of the acceptability of Risks to verify in turn whether the compliance with the *Design Requirements* was justified and/or continues to be justified and to drive development.
Post-Market Surveillance

Corrective and Preventive Actions (CAPA)

Requires a documented procedure for
- review of non-conformity
- determining cause
- evaluating need for action
- action taken
- CAPA records
- CAPA review and effectiveness

If required by national or regional authorities, ISO 13485 requires the Manufacturer to establish documented procedures to notify the regulatory authorities of those adverse events which meet the reporting criteria.

World Vigilance Reporting

<table>
<thead>
<tr>
<th>MDR/MDV:</th>
<th>EU</th>
<th>USA</th>
<th>Canada</th>
<th>Australia</th>
<th>Japan</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Purpose</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Reporting Criteria</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Report Recipient</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Reporting Timeline</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Reporting Form</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Reporting Information</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Investigation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Follow-Up Reports</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Report Recipient</th>
<th>EU</th>
<th>USA</th>
<th>Canada</th>
<th>Australia</th>
<th>Japan</th>
</tr>
</thead>
<tbody>
<tr>
<td>Competent Authority (29+)</td>
<td>FDA</td>
<td>HC</td>
<td>TGA</td>
<td>MHLW</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Reporting Timeline</th>
<th>EU</th>
<th>USA</th>
<th>Canada</th>
<th>Australia</th>
<th>Japan</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 days (ST)</td>
<td>5 days</td>
<td>10 days (I)</td>
<td>15 days (I)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 days (I)</td>
<td>30 days (NI)</td>
<td>30 days (NI)</td>
<td>30 days (NI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>30 days (NI)</td>
<td>10 days (I)</td>
<td>30 days (NI)</td>
<td>30 days (NI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(MS variations)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Reporting Form</th>
<th>EU</th>
<th>USA</th>
<th>Canada</th>
<th>Australia</th>
<th>Japan</th>
</tr>
</thead>
<tbody>
<tr>
<td>MEDDEV or CA Form</td>
<td>3500A</td>
<td>Advisory Form</td>
<td>Advisory Form</td>
<td>Initial</td>
<td></td>
</tr>
<tr>
<td>Web-Form</td>
<td>3417(Base)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Reporting Information</th>
<th>EU</th>
<th>USA</th>
<th>Canada</th>
<th>Australia</th>
<th>Japan</th>
</tr>
</thead>
<tbody>
<tr>
<td>Approximately the same</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Investigation</th>
<th>EU</th>
<th>USA</th>
<th>Canada</th>
<th>Australia</th>
<th>Japan</th>
</tr>
</thead>
<tbody>
<tr>
<td>Approximately the same</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Follow-Up Reports</th>
<th>EU</th>
<th>USA</th>
<th>Canada</th>
<th>Australia</th>
<th>Japan</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up Final</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3500A (Sup)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3417(Base)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Follow-up Final</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>As above</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monthly Final</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Challenge: Evolving regulations / guidelines (eg MEDDEV Rev 5 and GHTF proposal)
Summary

- Drugs and Devices are regulated very differently
  - Strategically & Tactically
  - Combination products present particular challenges
- Drug and Device regulation is converging
  - ICH vs ISO
  - Opportunities to learn from each other
e.g. Increased use of risk assessment and post-marketing feedback

Key to success – Keep talking!

Device Development and Design Control

THANK YOU

ANY QUESTIONS?

Paul Lafferty  
paul.lafferty@quintiles.com  
www.quintiles.com/QuintilesConsulting

Tim Chesworth  
tim.chesworth@astrazeneca.com  
www.astrazeneca.com