Comparative Overview of Other Medical Devices Regulatory Systems

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Dr David Jefferys

• Professional background and experience
Agenda

Overview of:
• European regulations
• Japan
• China
• India
The Regulation of Medical Devices in EU/EEA

New Approach Directives

- 90/35 EC  AIMD (active implantables)
- 93/42 EC  MDD (general medical devices)
- 98/79 EC  IVD (in vitro diagnostics)
- 2000/70 EC  stable derivatives of human blood and plasma derivatives
- Directive 2007/47 EC, technical revisions “updating directive” - Implemented March 2010
- 5 implementing Commission Directives (including TSE, breast implants, joint replacements)
- Advanced Therapies Regulation 1394/2007 EC
Key Features of Device Regulation in EU

- Relatively “young” legislation
- “New Approach” legislation and for all consumer products (except pharmaceuticals)
- The legislation reflects the dynamics of the medical device industry
Key Features of the Device Regulation

- Legislation sets out:
  - The ‘Essential Requirements’
  - Conformity assessment process
  - Obligations as manufacturers
- The role of the “Notified Bodies”
- The role of the Competent Authorities”
- Legislation underpinned by ‘nominative standards’
  - Meddev guidelines
Key Features of Device Regulation

- **Risk based classification of products**
  - Class I self regulation (and registration)
  - Class IIA (such as measuring devices, sterile products) selective QSR
  - IIB full QSR and targetted dossier review
  - III full design dossier review

- **Competent Authority Role**
- **Safeguard Clause**
Competent Authority Role

- Designation and supervision of Notified Bodies
- NBOG (EU Committee)
- Clinical trial controls (CTN)
- Compliance & enforcement role
- MSOG (EU Committee)
- Vigilance and User Reporting Adverse Incident Schemes
Notified Bodies

• Who are they?
• Scope of competence (annexes)
• Who supervises them?
  - National CAS
  - NBOG (EU level)
• Conflict of interests
• Who pays them?
• International CAB role FDA/Japan
Differences with FDA (510k)

- Class I devices are registered
- Compliance programme for Class I devices
- No replicate procedure
- The directive defines the assessment procedure
- User report scheme
- External Notified Body evaluation
Post-Marketing Surveillance in Europe

- Vigilance scheme - compulsory for manufacturers
  - Lead CA in Europe
  - Safeguard clause
  - Electronic reporting in some MS
  - Follows GHTF SG2 guidance
Post-Marketing Surveillance in Europe, contd

• User reporting system
  - ± Voluntary (most member states)
  - Healthcare professionals (± patient) reporting
  - Larger schemes
  - UK Liaison Officers
  - Linked to NHS in UK
Registries

• Present in many Member States
• Used for
  - Joint implants
  - Cardiac pacemakers
  - Heart valves
  - Coronary stents
  - Breast implants
  - Cephalic shunts
  - Some ATPs
• Use of electronic patient records
In Vitro Diagnostics (IVDs)

- Directive 98/79 EEC
- Annex 1 products
- Annex 2 products (defined list – includes all OTC direct to patient tests)
- Most biomarkers and genetic tests are annex 1 (self-certification)
- Commission Communication has proposed a move to a ‘risk based’ classification system
- “Home brew” test kits – no ‘gold standard’ for IVDs
Combination Products

• Drug/device
• Device/drug
• Diagnostic/drug combinations – companion diagnostics
• Concept of “Primary intended purpose”
Medical Devices administering a medicinal product

• The MDD applies if used separately (infusion pens, syringes)

• If the device and the medicinal product form a single integral product which is intended for use exclusively in the given combination (and is not reusable) the product is regarded as a medicine (pre-filled syringes/injectors)

• The relevant medicines agency has to contact a Notified Body or a Device CA
Medical devices incorporating a medical substance with an ancillary action

- These products are medical devices
- Examples (coated catheters, drug eluting coronary stents, steroid coated pacing wires, TACE products)
- Safety, quality and usefulness of the medical substance has to be verified by reference to the Directive 75/318/EEC as amended by a
  - Medicines CA
  - Involvement of the EMA
  - Position for new active substances
Directive 2000/70

Combination with a stable blood product:
Mandatory consultations with the EMA/CHMP
Drug Device Combinations

- Assess as pharmaceuticals
- Appropriate involvement of a device CA/experts
- The device component may be independently CE marked
- No Office of Combination Products
Advanced Therapy Products:
“Tissue Engineering”

• Background
• History of Human Tissue Regulation in Europe
• Current Situation
Advanced Therapy Products

- Regulation 1394/2007EC
- Covers
  - Viable human tissue products
  - Cell therapy products
  - Gene therapy products
- Implementation date - December 2008
- New committee CAT committee on advanced therapies, reports to CHMP
- Legislation covers allogeneic and autologous products
Figure 1: Application of ATMP Regulation (EC) 1394/2007

Cells and tissues for therapeutic use – application of the ATMP Regulation

Viable cells/tissues

- Human
- Animal

Non-viable cells/tissues

- Human
- Animal

Substantially manipulated?

- Yes
  - Principal action of product is pharmacological/metabolic/immunological?
    - No
      - Not ATMP
    - Yes
      - Not ATMP

'Homologous' use?

- No
  - ATMP
- Yes
  - Not ATMP

May be unregulated at EU level

Medical device
<table>
<thead>
<tr>
<th>Included in ATMP</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Product type</strong></td>
<td></td>
</tr>
<tr>
<td>Products containing ‘engineered’ cells or tissues:</td>
<td>• Autologous chondrocytes expanded in culture for reimplantation</td>
</tr>
<tr>
<td>• Cells or tissues that have been expanded, cultured or manipulated to produce the desired biological effect</td>
<td>• Allogeneic keratinocytes expanded in culture for burns treatment</td>
</tr>
<tr>
<td>• Cells or tissues administered to perform a function other than their normal function in the donor</td>
<td>• Fibroblast-derived dermal matrix for vascular repair</td>
</tr>
<tr>
<td>Products consisting of non-viable human or animal tissues, in which the intended function of the product is achieved by pharmacological, immunological or metabolic means</td>
<td></td>
</tr>
<tr>
<td>Products containing a combination of non-viable human or animal tissues and one or more medical devices, in which the intended function of the product is achieved by pharmacological, immunological or metabolic means</td>
<td>• Extracellular matrix derived from culture of human cells for delivery of cytokines or other proteins</td>
</tr>
<tr>
<td></td>
<td>• Extracellular matrix cultured on an implantable scaffold</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Excluded from ATMP</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Product type</strong></td>
<td></td>
</tr>
<tr>
<td>Products containing human cells or tissues that do not meet the definition of ‘engineered’ cells</td>
<td>• Unexpanded population of stem cells isolated from bone marrow or blood</td>
</tr>
<tr>
<td>Products containing non-viable human cells or tissues, that do not act principally by pharmacological, immunological or metabolic means</td>
<td>• Demineralised or purified human bone</td>
</tr>
<tr>
<td>Combination of non-viable human tissue and medical device in which the intended function of the product is achieved by mechanical or structural means</td>
<td>• Joint implant coated with human tissue that encourages ingrowth of recipient’s bone cells</td>
</tr>
<tr>
<td>Products containing non-viable animal cells or tissues in which the intended function of the product is achieved by mechanical or structural means</td>
<td>• Bovine collagen wound dressing</td>
</tr>
<tr>
<td>Combination of non-viable animal tissue and medical device in which the intended function of the product is achieved by mechanical or structural means</td>
<td>• Collagen or derivative coated onto a scaffold mesh</td>
</tr>
</tbody>
</table>
The Borderline

1. Medical Devices
2. Pharmaceuticals
3. Advanced Therapy Products
4. Cosmetics
5. Biocides
6. Foods (nutriceuticals)
7. Personal Protective Equipment
The Borderline

- Pharmaceuticals
- Foods
- Cosmetics
- PPE
- Medical Devices
- Advanced Therapy Products
- Biocides
Gives examples of borderline products which are classified as medicines/devices.

General rule: a relevant product is either regulated by the MDD or by the MPD (PPE).

Normally the procedures of both Directives do not apply cumulatively.

Examples:
- Bone cement and antibiotics
- Medicinal wipes
- Artificial saliva
Seeking Clarification

- Role of the Notified Body
- C A and the MDEG
  Medical Device Expert Group
  (e-mail consultations system)
Article 2.2

“In cases of doubt where, taking account of all its characteristics, a product may fall within the definition of a ‘medical product’ and within the definition of a product covered by other Community Legislation, the provisions of this Directive shall apply”
Recent Initiatives in PMDA and MHLW in Japan for Medical Device Approval
General Background

• Innovate 25 agenda
• New resources, new targets for PMDA
• Reducing the device/drug technology lag for Japan
• New policies of the Hatayoma Government
## Overview of Pre-market Regulation for Medical Devices

<table>
<thead>
<tr>
<th>GHTF CLASSIFICATION</th>
<th>PAL classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class A</td>
<td>Extremely low risk</td>
</tr>
<tr>
<td>Class B</td>
<td>Low risk</td>
</tr>
<tr>
<td>Class C</td>
<td>Medium risk</td>
</tr>
<tr>
<td>Class D</td>
<td>High risk</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Category</th>
<th>Pre-market regulation</th>
<th>Japanese MD Nomenclature 08/09</th>
</tr>
</thead>
<tbody>
<tr>
<td>General MDs (Class I)</td>
<td>Self declaration</td>
<td>1,195</td>
</tr>
<tr>
<td>Controlled MDs (class II)</td>
<td>Third party certification</td>
<td>1,786 (835 for 3rd Party)</td>
</tr>
<tr>
<td>Specially Controlled MDs (class III &amp; IV)</td>
<td>Minister’s Approval</td>
<td>742</td>
</tr>
</tbody>
</table>

- **GHTF Classification**
- **PAL Classification**
- **Japanese MD Nomenclature 08/09**
Third Party Registration
(12 designated certification bodies)

• MHLW/PMDA receives the application and validates it
• Third Party:
  - sent the design dossier
  - reviews the documentation (PAL Art 23-27)
  - recommends approval
  - undertakes inspection
• MHLW issues the certificate
Third Party Certification Standards

Standard for Products

Technical Standard for each MD (PAL Art.23-2)

= JIS (Japanese Industrial Standards) plus indication

Essential Principles (GHTF EP for all MD, PAL Art.41.(3))

= Detailed explanation to apply for each MD is shown

Standard for Quality Management System

Quality Management System Ministerial Ordinance

= Based on ISO 13485
Third Party Certification

**Application**

STED(*) document to explain conformity to Technical Standard and Essential Principles

(*Summary Technical Documentation, GHTF SG1N11)

**Evaluation/Certification**

Conformity to Technical Standard and Essential Principles

Conformity to Quality Management System

- On-site inspection and/or document review upon certification
- Follow-up inspection after certification
Future Direction of Third Party Certification System

- Currently 835(/1786) class II medical devices are designated for third party certification (FY 08)
- In principle, all Class II medical devices are expected to be transferred to the third party certification system (to be implemented by FY 2011)
## New IVD Regulation in Japan
### Notable Changes for IVD Regulation

<table>
<thead>
<tr>
<th>Under Old PAL</th>
<th>Under New PAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>No classification (All were subject to Ministerial approval)</td>
<td>New Classification (Class I, II and III)</td>
</tr>
<tr>
<td>No GMP/GMP-I</td>
<td>Mandatory Compliance to QMS/GQP/GVP</td>
</tr>
</tbody>
</table>
Major Changes in Registration Process and Requirements

- **Risk Based** Premarket Review System
  - Approval, third Party Certification and Self-Certification
- Quality System review as a Registration Process
  - Manufacturing Facility information and Audit
  - More detailed descriptions on manufacturing processes
- Adoption of various **Standards** and **Essential Principle** from GHTF
- Adoption of **Risk Analysis** including Risk Management System
- Dept of information/data has been increased!
# Risk Based Premarket Review System

<table>
<thead>
<tr>
<th>Class</th>
<th>Satisfy Standard?</th>
<th>Regulatory Path</th>
<th>Regulatory Clearance</th>
</tr>
</thead>
<tbody>
<tr>
<td>III (High Risk)</td>
<td>No applicable standard</td>
<td>PMDA (note)</td>
<td>Approval</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>PMDA</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>RCBs</td>
<td>Certification by the RCB</td>
</tr>
<tr>
<td>II (Medium Risk)</td>
<td>No</td>
<td>PMDA (note)</td>
<td>Approval</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>RCBs</td>
<td></td>
</tr>
<tr>
<td>I (Low Risk)</td>
<td>No</td>
<td>PMDA (note)</td>
<td>Approval</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>Self Certification</td>
<td>Notification</td>
</tr>
</tbody>
</table>

Note: Professional Board, which is called by MHLW, may be involved in some cases.
Requirements for IVDs

Addition to what’s been required under old PAL:

• Essential Principle (GHTF based)
  - QMS Compliance (IS13485:2003 based)
  - Risk Management system and Risk Analysis (ISO14971 based)
  - Needs to be included in submission documents

• Use of Standards
  - Correlation Standard for Approval
  - Correlation Standard for 3rd Party Review
  - Reference Material Standard
Medical Device Regulation in India

• Currently medical devices are controlled under the drugs law. Central and State level control
• New comprehensive medical device regulation has been proposed and consulted upon (schedule M-III)
• New proposals based on GHTF
## Classification

- Medical Devices to be classified as per their risk level and intended use:

<table>
<thead>
<tr>
<th>CLASS</th>
<th>RISK LEVEL</th>
<th>DEVICE EXAMPLES</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Low Risk</td>
<td>Thermometers/tongue depressors</td>
</tr>
<tr>
<td>B</td>
<td>Low-moderate Risk</td>
<td>Hypodermic Needles/suction equipment</td>
</tr>
<tr>
<td>C</td>
<td>Moderate-high Risk</td>
<td>Lung ventilator/bone fixation plate</td>
</tr>
<tr>
<td>D</td>
<td>High Risk</td>
<td>Heart valves/implantable defibrillator</td>
</tr>
</tbody>
</table>
Proposed Degree of Regulations as Medical Device Class

**Class A Medical Device**
- Conformity Assessment carried out by the manufacturer
- Manufacturing licence not required from Central Licensing Authority (CLAA)
- However, the manufacturer needs to be registered with the CLAA

**Class B Medical Devices**
- The Quality management system (QMS) to be certified by a Notified Body
- Based on the assessment by Notified Body CLAA shall issue NOC to manufacturer for such devices
Proposed Degree of Regulations as Medical Device Class

Class C Medical Device
• Certification by a Notified Body is required with regard to the design and manufacture of the device(s)
• The manufacturers are required to apply for a licence along with supportive documents with respect to safety and effectiveness of these devices
• Based on the certification of Notified Body and supportive documents manufacturing licence shall be issued by the CLAA

Class D Medical Devices
• Certification by a Notified Body is required with regard to the design and manufacture of the devices
• The manufacturer is required to apply for the licence with the supportive documents in respect of safety and effectiveness of these devices to CLAA
• Inspection of manufacturing such devices by CLAA and State Licensing Authority
• Based on Recommendations of joint inspections report and the certification by the Notified Body, the manufacturing licence will be issued by CLAA
Conformity Assessment Procedures

• Medical devices manufactured in India should, as a general rule, bear the ICAD mark (Indian Assessment Certificate)
• Each class of device should follow respective procedures given in the proposed schedule MIII for affixing the ICAC mark
• Manufacturer and/or the Notified Body verify the conformity assessment results if it has been carried out in accordance with the proposed schedule
Conformity Assessment Procedures

- The Notified Body may require, where duly justified, any information or data, which is necessary for establishing and maintaining the attestation of conformity in view of the chosen procedure.

- Conformity assessment Procedures as per SG1-N40:2006 of GHTF Guidelines have been recommended.
Conformity Assessment Procedures

- **ICAC** conformity assessment procedure outline. ICAC mandatory for devices to be sold in India.
- **Quality Management System** - Declaration of conformity would be issued on satisfactory assessment of QMS procedures.
- Class based conformity assessment procedures have been laid down with varying design and development verification procedures.
- **Class A** exempted from design and development procedures.
Notified Bodies

- Designer, manufacturer, supplier, installer or user of the device shall not be a member of Notified Body
- Notified Body to share all required information with the CLAA
- Guaranteed impartiality and professional secrecy of Notified Bodies
- Notified Body must take out civil liability insurance
- Manufacturer shall notify the CLAA of the Accredited Notified Bodies which they have designated for carrying out conformity assessment
Medical Device Regulation in China

- Mixture of central (SFDA) control and local provincial control
- Risk based system
- Class II and III products undergo sample testing at an approved laboratory (type testing)
- Selected products required to undergo evaluation in SFDA approved hospitals
Medical Device Regulation in China

- SFDA evaluation centre and technical committee
- Requirement for a local (Chinese) based distributor
- For overseas manufacturer attestation of approval by the country of origin
Concluding Remarks
Reserve Slides
Possible Options to Address Weaknesses in the Medical Device Legislation

- Retain ‘new approach’
- Strengthen evaluation procedures for high risk products
- Consolidation of expertise, COMD in EMEA
- Increased co-ordination of vigilance and market surveillance across EU
Possible Options to Address Weaknesses in the Medical Device Legislation, contd

- Extension of the scope to cover non-viable human tissues e.g. human collagen implants
- Enhanced approach to handling combination products
- Risk based evaluation of IVDs
- How to handle companion diagnostics