EU & FR MEDICAL DEVICES MARKET - ORIENTATION, CHALLENGES AND TRENDS: clinical tools

Faraj ABDELNOUR, Président ACIDIM

Tel (FR): +33 (0) 787 009 234
Tel (LE): +961 (0) 3 278 621
faraj.abdelnour@orange.fr / president@acidim.asso.fr / www.acidim.asso.fr
CE Marking Director AB Certification – Associate SYNERGUS

Ph.D. in Biomedical Engineering, helps medical devices manufacturer direct their efforts in the European regulatory, reimbursement & pricing environment, particularly in France and provides assistance for managing compliance with assessment and certification procedures throughout Europe (CE marking, European National regulatory conformity, vigilance, post-marketing, etc.).

Skills/Special Qualifications
Ph.D. in Biomedical Engineering in Drug Delivery system including implantable pumps for pain control, chemotherapy, spasticity treatments with Baclofen, and diabetic treatments with insulin.
Master’s Degree in Medical Imaging
Four years in Research Development for pharmaceutical laboratories;
Engineer in charge of French homologation, vigilance & post market surveillance on surgical devices (laser, lithotripter, HF, US) and Drug Delivery Systems;
Engineer in charge of relations with test laboratories at the French Ministry of Health;
Engineer in charge of official mission on behalf and on the name of the French Ministry of Health, and involved in a multiple expertise with French authorities and their partners (Social Security Organisation, Public Payers, Lab-test, etc) for reimbursement and health technology assessment;
Excellent knowledge of the European systems of healthcare and the disease management with technology assessment;
Good knowledge of the hospital environment, healthcare map, biomedical engineering, public tender rules, hospital medical project, etc…
International expert for the introduction of new biomedical technology through EU health systems
Presentation outline

• Introduction: need to clinical
  – Medicinal Product development & regulations
  – Medical Devices development & regulations

• From Technology to medical device marketing
  Regulatory and challenges

• Conducting medical devices studies in EU (case of France) process and key steps
Produits de Santé - *Healthcare products*

- Médicaments et matières premières - *Drug*
- Dispositifs médicaux et de diagnostic in vitro – *MD-AIMD & IVD*
- Biomatériaux et produits d’origine humaine ou animale (organes, tissus, cellules, PTA, et dérivés) – *animal, human origin derivatives*
- Thérapie génique et cellulaire – *gene & cell therapy*
- Produits sanguins labiles – *Blood derivatives products*
- Préparations hospitalières – *patient customized preparation*
- Aliments diététiques destinés à des fins médicales spéciales - *nutricaments*
- Cosmétiques - *cosmetics*
- Insecticides et produits anti-parasitaires à usage humain - *biocides*
- Désinfectants – *disinfectants*
- Etc………
Medicinal Product Regulations : History

• EU: Thalidomide disaster in the early 1960s

• US: Tragic mistake in the formulation of a children’s syrup in the 1930s and 260 childrens contract polio from 2 batches of polio vaccine that contained live polio virus in 1955

✓ Laws needed to protect the public health to prevent this type of disaster from occurring again

✓ A regulation needs to ensure that pharmaceutical companies have standards to follow in the development, manufacture, control and marketing of medicinal products

✓ Laws to assure “informed consent” of subjects participating in investigational drug studies
Medicinal Product Regulations

Legally binding acts:

- **EU:**
  - Directives which require national implementation
  - Regulations (on all members states) which take prevalence on national law
  - Decisions (on individual MS)

- **Non-legally binding acts:**
  - Guidelines, guidance for industry, opinions, points to consider and communications
  - GxPs Guidelines (GMPs, GCPs, GLPs)
  - ICH Topics and Guidelines, CPMP, national guidelines
  - *Not law, but adherence is strongly recommended*
Medicinal Product Regulations

Ensuring legislative requirements are met at development stage

Get the product on the market

Regulatory Affairs Coordination

Keep the product on the market

Ensuring legislative requirements are met at submission stage

Ensuring legislative requirements are met at early stage

Ensuring legislative requirements are met at late stage
Medicinal regulatory Affairs questions

• Step of drug development
  – Successful transition from the science to a legal regulatory document (SPC/Labeling)
    • Balance between science and law
    • Risk/benefit balance (quality, safety and efficacy)
    • Support R-D process
    • Evolving area

• Step of clinical trials
  – Weighting the pros against cons
  – Approval from regulatory authorities following submission
  – Provides a scientific safety net for subjects
Role of the Regulatory Authorities

- Manufacturers
- Market Authorisation holder
- Importers/Wholesalers/Retailers
- Government
- Experts
- Prescribers
- Patients/Consumers
Role of the Regulatory Authorities In E.U.

EMEA EMA

Management Board

Secrétariat

CHMP

European Parliament → Regulations Directives Decisions

Council of Ministers

EUROPEAN COMMISSION

Implementation of Regulations Directives Decisions

NATIONAL AGENCIES

1 representative per MS

WHO

EP

Control lab

MHRA

AFSSAPS

ANSM

PEI
Role of the Regulatory Authorities

To safeguard and protect the public health with regard of medicinal products

- Determine the risk/benefit ratio of the product by assessing its quality, safety, and efficacy
- Licensing of manufacturers, importers, distributors, wholesale and retail outlets
- Marketing authorization (product approval)
- Provision of medicinal products information and monitoring of the promotion and advertising
Role of the Regulatory Authorities

• Monitor the adverse drug reactions (pharmaco vigilance)
• Authorization of clinical trials
• Quality control laboratory testing and release
• Ensuring respect of legislation
• Development of new regulations and guidance documents for industry
• Development of standard / reference methods and products
Every medicinal product which is promoted for sale in the EU must hold a marketing authorisation.

Procedures for approval

- **MRP/DP**
  - 2 steps (national/MR) apply to each MS (25) National authorisations

- **Centralised**
  - 1 step apply to EMEA 1 EU-wide authorisation

- **National**
  - 1 step apply to 1 MS 1 National authorisation
Medicinal Product Regulations

Regulatory Affairs & Product Development

**Pharmaceutical R&D**
- Pre-clinical Phases
  - Regulatory Consulting
  - Critical Data review
    - Gap analysis
    - Non-clinical strategy
    - Scientific advice
  - IB production

**Clinical Phases**
- Phase I
- Phase II
- Phase III
  - Compilation of Clinical Trial Applications, RTL, IMPD
  - Regulatory Consulting
    - Gap analysis vs EU Guidelines
    - Clinical strategy and development plan
    - Scientific advice & ODDA
  - Compilation of Common Technical Document for Marketing Authorization applications (on completion of pivotal Phase III)

**Post Approval Surveillance and Optimization**
- License variation applications
  - New formulations
  - New indications
  - Change in manufacturing
  - Process, stability, raw Materials
  - Labeling changes
- Urgent safety restrictions

**Phase IV**

**Technology Assessment**
- Technical & clinical development
- Regulatory
- Marketing & reimbursement
Contribution of Medical Technology to Life Expectancy

**Medical Device Sector**

Potentially > 400,000 devices on the market (>10,000 families)

**Contribution of Medical Technology to Life Expectancy**

- **Infant mortality** 1960 - 2000  - 81 %
- **Life expectancy at birth** 1960 - 2000  + 13 %

*OECD Health Data 3rd Ed*

*Significant contribution in life expectancy of 8 years in Europe in last 30 years*
Medical Device Sector

Potentially > 400,000 devices on the market (>10,000 families)

- Vascular implants
- Hearing Aids
- Intra-Ocular Lenses
- Dialysis Equipment
- Imaging Equipment
- Stimulators
- Catheters
- Wound Dressings
- Tongue Depressors
- Heart Valves
- Physiological Monitors
- Sutures

Orthopaedic Implants
- Contact Lenses
- Physiotherapy Equipment
- Diagnostic Devices
- Radiation Therapy Equipment
- Radiation Therapy Simulators
- Drug/nutrient Delivery
- Cosmetic Prostheses
- Contraceptives
- Thermometers
- Lancets
- Sterilisers
- Endoscopes
- Filters

Surgical Instruments
- Bone Cements
- Spectacles
- Operating Tables
- Artificial Limbs
- Stethoscopes
- Surgical gloves
- Defibrillators
- Hospital Beds
- Aspirators
- Swabs
Medical Device Sector

Potentially > 400,000 devices on the market (>10,000 families)

Contribution to Healthcare

- Prevention
- Screening
- Diagnosis
- Treatment
- Rehabilitation
- Improvement of Quality of Life
- Reducing the Cost of Healthcare
Differences between drugs and medical devices
PRODUCTS

- more than 10,000
- designed to perform certain functions based on quality, safety and performance
- generally based on mechanical, electrical and/or materials engineering
- generally act by physical means
- continuous innovation and iterative improvements based on new science, technology and available materials
- short product lifecycle and investment recovery period (typically 18 months on the market)
- the majority of new products typically bring added functions and clinical value based on incremental improvements
- high cost of distribution
- high cost of user training and education
- provision of service and maintenance for high tech devices
- often integral to clinical procedure, so user education and training are essential for safe and effective use
- limited number
- development by trial and selection on basis of quality, safety and efficacy
- based on pharmacology and chemistry
- now encompassing biotechnology and genetic engineering
- biologically active: effective when absorbed into the human body
- continuous innovation and some improvements based on new science and technology
- extensive product lifecycle and long investment recovery period
- low distribution cost
- in most cases, no service and maintenance
- training required for use much less intensive than for high tech medical devices

EU REGULATION

- based on the "New Approach" (CE marking)
- applicable processes depend on risk-category
- government-appointed Notified Bodies certify the conformity assessment procedures
- improvements often result from user feedback
- prescriptive approach: pre-market approval/licensing of individual product
Valuation

FROM IDEA TO MARKET

RISK

VALUE ADDED

MARTKET

IDEA

Research (R&D)
IP

PRODUCT

PROTOTYPE

Development (R&D)
IP
Regulatory
Manufacturing issues

Sales & Marketing
Medical Marketing
Reimbursement
Manufacturing
**From Idea to Drug**

<table>
<thead>
<tr>
<th>Research stage</th>
<th>Testing stage</th>
<th>Development stage</th>
<th>Commercialisation</th>
</tr>
</thead>
<tbody>
<tr>
<td>IP submission</td>
<td>5 years</td>
<td>10 years</td>
<td>15 years</td>
</tr>
<tr>
<td>10 years of R&amp;D</td>
<td></td>
<td></td>
<td>20 years</td>
</tr>
</tbody>
</table>

- Long
- Pass/Fail

*IP extension Maxi 5 years
End of IP*
Evolution of MD Development Process

**VALUATION**
- Increases with laboratory, preclinical, and clinical data

**PROOF OF CONCEPT**
- Iterative process

**REGULATORY TESTING**
- Linear process

**QUALITY PROCESS**
- Full Quality System
- Minimal Quality Level
Medical Devices

European and Worldwide Growth

Trends and Niche Products
Medical Devices Market

- Japon: 14.6%
- Reste du monde: 19.0%
- Etats-Unis: 42.2%
- Europe: 24.2%

Données EUCOMED
European Medical Technology Market Position

- Europe 2nd largest market after USA, followed by Japan
- Devices no longer overshadowed by pharmaceuticals - some countries devices outstrip pharma
- Public expenditure believed increasing - offset against benefits - net effects positive
- Highly innovative
- Last Commission EU competitiveness study 2003 - next report expected July 15
European Medical Technology Market Split %

Source: Eucomed Member Associations, Medistat and Eucomed calculation
# Expenditure in Medical Technology and Total Healthcare Expenditure

<table>
<thead>
<tr>
<th>Country</th>
<th>Population 1000</th>
<th>THE in Bn Euro</th>
<th>THE/GDP in %</th>
<th>EMT in Bn Euro</th>
<th>EMT/THE in %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Austria</td>
<td>8.092</td>
<td>16.9</td>
<td>7.9</td>
<td>0.73</td>
<td>4.3</td>
</tr>
<tr>
<td>Belgium</td>
<td>10.397</td>
<td>22.7</td>
<td>9.0</td>
<td>0.82</td>
<td>3.6</td>
</tr>
<tr>
<td>Cyprus</td>
<td>728</td>
<td>0.6</td>
<td>6.1</td>
<td>0.03</td>
<td>4.5</td>
</tr>
<tr>
<td>Czech Republic</td>
<td>10.211</td>
<td>4.7</td>
<td>7.3</td>
<td>0.37</td>
<td>7.9</td>
</tr>
<tr>
<td>Denmark</td>
<td>5.398</td>
<td>15.2</td>
<td>8.6</td>
<td>0.87</td>
<td>5.7</td>
</tr>
<tr>
<td>Estonia</td>
<td>1.351</td>
<td>0.4</td>
<td>5.8</td>
<td>0.04</td>
<td>10.0</td>
</tr>
<tr>
<td>Finland</td>
<td>5.220</td>
<td>9.4</td>
<td>7.0</td>
<td>0.45</td>
<td>4.8</td>
</tr>
<tr>
<td>France</td>
<td>59.896</td>
<td>139.0</td>
<td>9.5</td>
<td>9.00</td>
<td>6.5</td>
</tr>
<tr>
<td>Germany</td>
<td>82.545</td>
<td>221.2</td>
<td>10.7</td>
<td>19.00</td>
<td>8.6</td>
</tr>
<tr>
<td>Greece</td>
<td>11.047</td>
<td>12.2</td>
<td>9.4</td>
<td>0.54</td>
<td>4.4</td>
</tr>
<tr>
<td>Hungary</td>
<td>10.115</td>
<td>3.9</td>
<td>6.8</td>
<td>0.36</td>
<td>9.2</td>
</tr>
<tr>
<td>Ireland</td>
<td>4.025</td>
<td>7.4</td>
<td>6.5</td>
<td>0.36</td>
<td>4.9</td>
</tr>
<tr>
<td>Italy</td>
<td>57.482</td>
<td>106.7</td>
<td>8.6</td>
<td>6.16</td>
<td>5.8</td>
</tr>
<tr>
<td>Latvia</td>
<td>2.319</td>
<td>0.5</td>
<td>5.8</td>
<td>0.06</td>
<td>11.5</td>
</tr>
<tr>
<td>Lithuania</td>
<td>3.447</td>
<td>0.8</td>
<td>5.7</td>
<td>0.06</td>
<td>8.3</td>
</tr>
<tr>
<td>Luxembourg</td>
<td>451</td>
<td>1.2</td>
<td>5.6</td>
<td>0.05</td>
<td>4.1</td>
</tr>
<tr>
<td>Malta</td>
<td>400</td>
<td>0.9</td>
<td>8.8</td>
<td>0.02</td>
<td>1.7</td>
</tr>
<tr>
<td>Netherlands</td>
<td>16.258</td>
<td>38.2</td>
<td>8.9</td>
<td>2.50</td>
<td>6.5</td>
</tr>
<tr>
<td>Norway</td>
<td>4.514</td>
<td>15.0</td>
<td>8.0</td>
<td>0.93</td>
<td>6.2</td>
</tr>
<tr>
<td>Poland</td>
<td>38.194</td>
<td>12.5</td>
<td>6.3</td>
<td>0.77</td>
<td>6.1</td>
</tr>
<tr>
<td>Portugal</td>
<td>10.480</td>
<td>11.3</td>
<td>9.2</td>
<td>0.60</td>
<td>5.3</td>
</tr>
<tr>
<td>Slovak Republic</td>
<td>5.381</td>
<td>1.3</td>
<td>5.7</td>
<td>0.11</td>
<td>8.6</td>
</tr>
<tr>
<td>Slovenia</td>
<td>1.997</td>
<td>1.9</td>
<td>8.0</td>
<td>0.13</td>
<td>7.1</td>
</tr>
<tr>
<td>Spain</td>
<td>40.978</td>
<td>48.8</td>
<td>7.5</td>
<td>3.00</td>
<td>6.1</td>
</tr>
<tr>
<td>Sweden</td>
<td>8.975</td>
<td>21.3</td>
<td>8.7</td>
<td>1.08</td>
<td>5.1</td>
</tr>
<tr>
<td>Switzerland</td>
<td>7.233</td>
<td>30.5</td>
<td>11.1</td>
<td>1.35</td>
<td>4.5</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>59.518</td>
<td>121.3</td>
<td>7.6</td>
<td>5.89</td>
<td>4.8</td>
</tr>
</tbody>
</table>

**Europe Total/average**

<table>
<thead>
<tr>
<th>Country</th>
<th>Total Expenditure</th>
<th>THE in Bn Euro</th>
<th>THE/GDP in %</th>
<th>EMT in Bn Euro</th>
<th>EMT/THE in %</th>
</tr>
</thead>
<tbody>
<tr>
<td>United States</td>
<td>446.652</td>
<td>845.8</td>
<td>8.6</td>
<td>55.20</td>
<td>6.4</td>
</tr>
<tr>
<td>European Union</td>
<td>294.797</td>
<td>1553.3</td>
<td>13.9</td>
<td>79.281</td>
<td>5.1</td>
</tr>
</tbody>
</table>

Source: OECD, European Commission, Eucomed Member Associations and Medistat
Import and Exports of Medical Technology

Source: Eucomed Member Associations and Medistat
Orthopedics market:

Reconstructive joint replacement: 27%
Spinal implants: 26%
Bone Graft: 10%
Arthroscopy: 9%
Trauma: 7%
Bone growth stimulators: 2%
Powered instruments: 2%
Soft goods: 6%
CMF: 3%
Other: 7%
Orthopedics market (2010):

Germany: 25% EU = 632 M$
France: 20% EU = 499 M$
UK: 15% EU = 372 M$
Italy: 14% EU = 349 M$
Spain: 10% EU = 236 M$
Scandinavia: 4% EU = 120 M$

US: 58% = 7.1 B$
Europe: 20% = 2.45 B$
Asia: 15% = 1.9 B$
Americas: 7% = 0.9 B$

Surgical Dynamics (Tyco)
Zimmer (BMS)
Depuy (J&J)
Stryker
Sulzer Medical
Synthes – Stratec
Medtronic Sofamor Danek
Biomet
Smith & Nephew
Hanger
Orthofix International
OrthoLogic
Osteotech
Advanced Tissue Sciences
Integra
Interporre Cross International
Bionx
Corin
Raymedica
Wright Medical Thechnology
Les 25 acteurs industriels mondiaux

**top 25 (60% du CA mondial)**

J&J (US)
GE (US)
Siemens MS (Germany)
Medtronic (US)
Baxter (US)
Covidien (US)
Roche (Switz)
Becton Dickinson (US)
Abbott (US)
Stryker (US)
Olympus (JPW)
Zimmer (US)
Smith & Nephew (US)
Becton Coulter (US)
Cardinal health (US)
Olympus (JPW)
3M healthcare (US)
St Jude medical (US)
Beckman Coulter (US)
Terumo Med (JPW)
Fresenius MC (Germany)
Alcon (US)
Carestream (Can)
C.R. Bard (US)
Les 30 premiers acteurs en France : une entreprise sur cinq est nationale

les 30 premiers acteurs en France
CA > 100M€
représentent 10,5M€ CA
**European Contracting Member States**

**European Union (EU) - 27**
Austria, Bulgaria, Belgium, Cyprus, Czech Republic, Denmark, Estonia, France, Finland, Germany, Greece, Hungary, Italy, Ireland, Netherlands, Latvia, Lithuania, Luxembourg, Malta, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, UK

**European Economic Area (EEA) - 28**
EU + Iceland, Liechtenstein, Norway, Switzerland

**European Free Trade Area Association (EFTA) - 4**
EU + Iceland, Liechtenstein, Norway, Switzerland

**European Economic Area (EEA) - 28**
EU + Iceland, Liechtenstein, Norway

**EU Candidates + 2**
Turkey, Croatia
EC Medical Devices Directives

To mitigate in part the **RISKS** posed by **MEDICAL DEVICES** we have devised **PRE / POST-MARKET CONTROLS:**

- **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
- **2005/50/EC** Reclassification of orthopaedic articulation devices
- **2007/47/EC** Amendments of 90/385 & 93/42

Medical Devices Directive 93/42/EEC

Scope and Definitions

Medical Device: Any instrument, apparatus, appliance, material software or other article, including software required for its proper functioning, whether used alone or in combination, intended by the manufacturer to be used solely or principally for the purpose of:

- diagnosis, prevention, monitoring, treatment, alleviation of disease
- diagnosis, monitoring, treatment or alleviation of injury or handicap
- investigation, replacement or modification of the anatomy or of a physiological process
- control of conception

and 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

MDD Article 1.2(a)
Medical Devices Directive 93/42/EEC

Scope and Definitions

- Medical devices and their accessories
- MDD excludes:
  - AIMDs, IVDs covered by own Directives
  - medicinal and cosmetic products
  - human blood, blood products, plasma, or cells, or devices incorporating them (but not HBD)
  - human transplants, tissues or cells
  - animal tissues or cells unless rendered non-viable
  - personal protective equipment
ANALYSE DEVICE
INTENDED PURPOSE

ESSENTIAL REQUIREMENTS

DETERMINE CONFORMITY

• In vitro Tests
• In vivo Tests

TECHNICAL DOCUMENTATION

PRODUCTION

• PMS
• VIGILANCE

CLASSIFY DEVICES

CONFORMITY ASSESSMENT (MDD ANNEXES II-VII)

CLINICAL EVALUATION

EC DECLARATION OF CONFORMITY

CONFORMITY ASSESSMENT

CE MARKING

CONFORMITY ASSESSMENT

EC DECLARATION OF CONFORMITY

CE MARKING

NATIONAL MDD TRANSPOSITIONS
COUNTRY ISSUES
28 EEA MEMBER STATES + SWITZERLAND

• Labelling
• Registration

Medical Devices Directive 93/42/EEC

Structure
Medical Devices Directive 93/42/EEC

Single European Market

27 Different Versions

29 with EEA + Switzerland

29 Competent Authority Interpretations (note + 90 counting State authorities)

+ 75 Notified Bodies
Medical Devices Directive 93/42/EEC

The PLAYERS:

- Manufacturer
  - Registrations
  - Surveillance
  - Vigilance
  - Enforcement

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

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

- Inspection
- “Certification”
- Accreditation
- Consultation
- Surveillance
- Enforcement

Slide 38
## Comparison Regulations:

<table>
<thead>
<tr>
<th></th>
<th>EEA</th>
<th>USA</th>
<th>JAPAN</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Regulator (enforcement)</strong></td>
<td>CA’s, NB’s</td>
<td>FDA</td>
<td>Prefecture</td>
</tr>
<tr>
<td><strong>Authorisation</strong></td>
<td></td>
<td>FDA Centre</td>
<td>MHLW</td>
</tr>
<tr>
<td><strong>Definitions, Classification</strong></td>
<td>Safety and Performance</td>
<td>Safety and Effectiveness</td>
<td></td>
</tr>
<tr>
<td><strong>General Requirement</strong></td>
<td>Essential Requirements</td>
<td>Prescribed</td>
<td></td>
</tr>
<tr>
<td><strong>Specific Criteria</strong></td>
<td>Options</td>
<td>510K, PMA</td>
<td></td>
</tr>
<tr>
<td><strong>Conformity Assessment</strong></td>
<td>Self-regulation</td>
<td>Notification and Licensing</td>
<td></td>
</tr>
<tr>
<td><strong>Emphasis</strong></td>
<td>Optional (but not available for Class I)</td>
<td>Mandatory Class II+III (some Class I)</td>
<td>Mandatory (but excludes most Class I)</td>
</tr>
<tr>
<td><strong>Full Quality System (design and production)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Impact of MDD Revisions
(as defined by 2007/47/EC amending 93/42/EEC)

Conducting Medical Device Studies
Impact of MDD Revisions

Setting the Scene:
Timelines MDD Revision (as defined by 2007/47/EC amending 93/42/EEC)

- **05 September 2007**: Date of Directive 2007/47/EC
- **21 September 2007**: Date of Publication in the OJEU
- **11 October 2007**: Date that Directive enters into force (ref. Article 5)
- **21 December 2008**: Final Date by which EU Member States need to have transposed the Directive into corresponding National Legislation (ref. Article 4, 1st paragraph)
- **21 March 2010**: Directive becomes mandatory throughout EU; "old MDD" no longer applicable (ref. Article 4, 2nd paragraph)
Impact of MDD Revisions
(as defined by 2007/47/EC amending 93/42/EEC)

Assess Relevant Changes to MDD Impacting manufacturer

Clinical Data

&

Conformity Assessment Procedures,
Device – Drug Combinations,
Labelling,
PMS,
Miscellaneous
Impact of MDD Revisions
(as defined by 2007/47/EC amending 93/42/EEC)

Changes to MDD Impacting manufacturer: Clinical Data

1. Added Definition [ref. Article 1(k)]
2. Additional Requirements [ref. Art. 15 and Annex]
3. Significant Amendment [ref. Annex X]
5. More Explicit reference [ref. Annex II, 3.2(c)]
Impact of MDD Revisions
(as defined by 2007/47/EC amending 93/42/EEC)

Changes to MDD Impacting manufacturer: Clinical Data

1. **Added Definition** [ref. Article 1(k)]

k) “données cliniques”:
informations relatives à la sécurité et aux performances obtenues dans le cadre de
l'utilisation d'un dispositif. Les données cliniques proviennent:
   - des investigation(s) clinique(s) du dispositif concerné, ou

   - des investigation(s) clinique(s), ou d'autres études citées dans la littérature scientifique,
d'un dispositif similaire pour lequel l'équivalence avec le dispositif concerné peut être
démontrée, ou

   - des rapports, publiés ou non, relatifs à une autre expérience clinique acquise sur le
dispositif ou un dispositif similaire pour lequel l'équivalence avec le dispositif concerné
peut être démontrée.”

Impact of MDD Revisions
(as defined by 2007/47/EC amending 93/42/EEC)

Changes to MDD Impacting manufacturer: Clinical Data

2. **Additional Requirements** [ref. Art. 15 and Annex]

7. Le fabricant ou son mandataire notifie aux autorités compétentes des États membres concernés la fin de l'investigation clinique, en justifiant, le cas échéant, l'arrêt prématuré de l'investigation. Si l'investigation clinique a été interrompue prématurément pour des raisons de sécurité, la notification est adressée à tous les États membres et à la Commission. Le fabricant ou son mandataire tient le rapport visé à l'annexe X, point 2.3.7, à la disposition des autorités compétentes.

*More Transparency across EU / Status Clinical Investigations no longer Confidential*
Impact of MDD Revisions
(as defined by 2007/47/EC amending 93/42/EEC)

Changes to MDD Impacting manufacturer: Clinical Data

3. Significant Amendment [ref. Annex X]

Annex X, pt. 1.1 amended

Section 6 of Annex I, must be based on clinical data.
For High Class Devices clinical study becomes Default. Rigorous Justification required if alternative

Annex X, new pt. 1.1
More Rigorous Substantiation expected if clinical data are not used …but remains possible.

Annex X, pt. 2.3.5 amended
Will require additional and prompt SAE reporting (also non-device related) to additional CA’s on top of the CA of the country where the SAE occurred
Impact of MDD Revisions
(as defined by 2007/47/EC amending 93/42/EEC)

Changes to MDD Impacting manufacturer: Clinical Data


“Demonstration of conformity with the essential requirements must include a clinical evaluation in accordance with Annex X.”

Question if the “must” is not in contradiction with quoted statement in Annex X, pt. 1.1d (previous slide!)

Manufacturers need to Update their Essential Requirements Checklist (Note: ER 14 needs to be deleted at same time and other ER’s updated as needed).
Impact of MDD Revisions
(as defined by 2007/47/EC amending 93/42/EEC)

Changes to MDD Impacting manufacturer: Clinical Data

5. More Explicit reference [ref. Annex II, 3.2(c)]

“The procedures for monitoring and verifying the design of the products, including the corresponding documentation, and in particular: [...] the clinical evaluation referred to in Annex X”.

Take into account when compiling Design Dossier / Technical File.
Impact of MDD Revisions
(as defined by 2007/47/EC amending 93/42/EEC)

Changes to MDD Impacting manufacturer: Clinical Data

5. More Explicit reference [ref. Annex II, 3.2(c)]

“The procedures for monitoring and verifying the design of the products, including the corresponding documentation, and in particular: [...] the clinical evaluation referred to in Annex X”.

- Take into account when compiling Design Dossier / Technical File.
Impact of MDD Revisions
(as defined by 2007/47/EC amending 93/42/EEC)

Take home message
Relevant Changes to MDD Impacting manufacturer

The need of Clinical Data

Clinical Investigations are needed
Status Clinical Investigations no longer “Confidential”
More Transparency across EU

- La conformité aux EE doit inclure une évaluation clinique (EE 6bis)
- DMIA et DM de classes III doivent faire l’objet d’investigations cliniques sauf si le recours aux données existantes peut être dûment justifié
- Mise à jour de l’évaluation clinique avec les données obtenues par la surveillance après commercialisation
- Si pas de suivi clinique post-commercialisation : justification nécessaire
Directive 2007/47/CE
(6/11) : REGLEMENTS

• Propositions publiées le 26 septembre 2012
  (2012/0266 relatif aux DMs et DMIAJs) et
  (2012/0267 relatif aux DMDIV)
• Pourraient être adoptées en 2014 ?
• Applicable 3 ans après publication au JO
  (dès 2017?)
• Règlement ≠ Directive :
  – Pas de transposition, donc pas d’interprétation possible!
Directive 2007/47/CE
(7/11) :

• Chapitre VI : Articles 49 à 60
  – Evaluation clinique & investigation clinique
    • + détaillé que dans les directives actuelles
    • Enregistrement électronique des investigations cliniques
    • Délai soumission : max 35 jours + 6 jours
    • Si plusieurs soumissions en UE : possibilité d’une soumission unique à l’échelle Européenne
Directive 2007/47/CE

(10/11):

• Annexe XIII:
  – Evaluation clinique et suivi clinique post-commercialisation
  – Exigences mieux détaillées que dans les directives

• Annexe XIV:
  – Investigations cliniques
    ➢ Description des méthodes
    ➢ Documentation
    ➢ Contenu IB / Protocole
New System – ANSM Authorisation

Insurance

(CPH Art. R. 1121-7)

Minimum:

1,000,000 € per victim
6,000,000 € per research protocol
10,000,000 € for total claims during one insurance year for several research protocols
New System – ANSM Authorisation
Main issues to consider

• According to a ANSM presentation, based on experience

- Incomplete data on the MD;
- Inadequate patient selection criteria;
- Duration of patient follow-up: not adequate for the study objectives;
- Patient information regarding the risks
New System – ANSM Authorisation

Experience from pilot phase

Based on ANSM experience:

Of 346 declarations made, 83 were done according to the pilot phase:

- 76% were given a favourable opinion at the first round;
- 22% of cases:
  - protocol changes suggested or
  - changes to the patient information
  - or supplementary information requested.
- Only 2% non-authorisation issued
The future

• New EU regulation for drug clinical trials coming into publication: changes within the existing system
• The new regulation regarding MD/AIMD & IVD will for sure make some changes within the present law and mainly for observational (non interventional) studies?
Thanks for attention

Questions?
Investigation clinique des dispositifs médicaux pour sujets humains
– partie 1: Exigences générales

Clinical investigation of medical devices for human subjects
– Part 1: General requirements
Investigation clinique des dispositifs médicaux pour sujets humains
– Partie 2 : Plans d’investigation clinique

Clinical investigation of medical devices for human subjects
– Part 2: Clinical investigation plans