“Impact of the new Medical Devices Regulations (MDR) on US Medical Devices Manufacturers exporting to Europe”

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European Parliament votes on Pre Market Authorization (PMA) elements in high risk device market access

Today, (22 October 2013) the European Parliament made a decision in the first Reading on the future of medical device regulations in Europe. The proposed amendments by the committee on Environment, Public Health and Food Safety (ENVI) and other working groups of the parliament created strong and fierce debates in preparation for today’s vote. A significant 1179 amendments were filed on the proposed Medical Device Regulation from the three groups on Employment and Social Affairs (EMPL), Internal market and Consumer Protection (IMCO) and ENVI working on the proposals, and another 532 on the In Vitro Diagnostics Regulation. The initial amendments were narrowed down to 30 MDD and 27 IVD consolidated and compromise amendments, that were mostly endorsed in the ENVI vote on September 25, including some of the remaining 1711 amendments. Subsequently further negotiations between political parties took place to file a further 30 consolidated amendments, that together with the compromises reached in the ENVI committee on 25 September, formed the basis of today’s plenary discussion and subsequent vote.

Today, new amendments were brought into the debate to refine the compromises from the earlier ENVI proposals. The amendments were proposed from various political groups, individually or combined. The topics still under debate included patient welfare and the prevention of fraudulent practice, the supervision on Special Notified Bodies, the scrutiny process of second guessing the Notified Bodies review, increased transparency, , ethical approval on clinical studies and genetic testing. Most of the debating surrounded the notorious compromise amendments 166, the extensive article where rapporteur Dagmar Roth Behrendt has tried to combine elements of her earlier Pre-Market Approval system for high risk devices under control of the European Medicines Agency (EMA), with the scrutiny procedure previously suggested in the original Commission proposal of 26 September 2012. Combining these elements would make for a highly bureaucratic system, where close to 600 clinicians would need to be employed by EMA to second guess the certification reviews made by as many clinical experts utilised by the so-called ‘Special Notified Bodies’.
EU Parliament 1\textsuperscript{st} Reading of MDR on October 22\textsuperscript{nd} 2013

Background:

- 1179 amendments have been filed by 3 EU Parliament committees
  - Employment and Social Affairs (EMPL)
  - Internal market and Consumer Protection (IMCO)
  - Environment, Public health and Food Safety (ENVI)
- 532 amendments have filed on “In Vitro Diagnostics Regulation”
- Narrowed down to 30 MDR and 27 IVD consolidated amendments
- New amendments were brought into the debate to refine the compromises from the earlier ENVI proposals, among those ... \textit{ethical approval on clinical studies and genetic testing}.
- Notified Bodies shall invest in having own in-house clinical staff
- Approval costs will for high risk devices, implants and drug-delivery devices will increase significantly
Next Step in the the political process

To be expected:

- Negotiations for at least 16 more month between
  - EU Member States (Council of Ministers)
  - EU Commission
  - EU Parliament
- Rapporteurs for MDD (Dagmar Roth-Behrendt) and IVD (Peter Liese) are pushing hard to get earlier resolution in the triilogue debates (< Mai 2014)
- Chances of new regulations being endorsed before summer 2014 have significantly increased by this calendar week
EU Legislation process

- EU Commission: MDR proposal
- EU Parliament: Amending MDR
- EU Council = 27 States: Amending MDR
- EU Parliament 1st Reading Position
- Common Position
- Final text 2nd reading OR EU Elections

Sept 2012 to March 2013 to Sept 2013 to Dec 2013 to May 2014 to June 2014
Current Position of the EU Parliament \textit{from February 26 hearing}
Which new Regulations?

- Proposal (542/2012) for Medical Devices
  - to replace Directive 93/42/EEC
  - and 90/385/EEC regarding active implantable medical devices
- Proposal (541/2012) for IVVs

Why?

- EU countries interpret and implement the current rules in different ways
- Lack of public access to information on MD assessment, clinical evidence, risk/benefit ratio
- Need for same high health & safety standards for all EU member states
- recent scandals: faulty silicone breast implants; problems with metal-on-metal hip replacements
What exactly will change?

- **Wider, clearer scope for EU legislation** (e.g. include implants for aesthetic purposes)
- **Stronger supervision of assessment bodies** (by national authorities)
- **More powers for assessment bodies** to ensure (regular checks on mfr., unannounced factory inspections)
- **Clearer rights & responsibilities** for mfr., importers; distributors, apply to diagnostic services and internet sales
- **Extended EUDAMED database** with publicly available information on medical devices
- **Better traceability** throughout the supply chain
- **Stricter requirements for clinical evidence**
- **Updated classification rules** dividing medical devices into 4 different risk categories
- **Better coordination between EU-Commission and national surveillance authorities**
- **Incorporation of International guidelines into EU law.**
What about Medical Devices and IVDs imported from outside the EU?

- Medical devices and IVDs produced in a third country and imported into the EU are subject to the same rules as medical devices produced within the EU.

- The Commission is actively involved in initiatives for international harmonization in the field of medical devices and IVDs such as
  - the former Global Harmonization Task-Force (http://www.ghtf.org/) and
  - the new International Medical Device Regulators Forum (http://www.imdrf.org/).

- The Commission proposals incorporate guidelines developed at international level into EU law with a view to converging the regulatory requirements in major economies.

**EU propose** *(Sept. 26 2012)*

**New Regulations for Medical Devices to be**

safe, effective, innovative

**freely & fairly traded in EU**

**Target for adoption: 2014**

**Come into force: 2015-19**
Clinical evidence need review by independent clinical experts

- **EC Proposal: Chapter VI: Clinical evaluation and clinical investigations**
  - Article 49: Clinical evaluation
  - Article 52: Registration of clinical investigations
  - Article 53: Electronic system on clinical investigations
  - Article 55: Substantial modifications to a clinical investigation

- **Annex XIII and XIV**
  - Required clinical data should be able to clearly demonstrate that devices perform well and are safe for patients when used by a physician as intended by their manufacturer.

- **Recent improvements by Directive 2007/47/EC**
  - Included the clear requirement that all devices have clinical evidence to demonstrate safety and furthermore that all implantable and class III devices must undergo clinical trials.

- **The Commission has built on this Directive by adding**
  - More detail for clinical requirements (Art. 50);
  - Centralized system for notifications and reporting of severe adverse events (Art. 53);
  - Increased protection of subjects undergoing clinical investigations (Art. 50, 52, 59);
  - Extended post-market clinical follow-up by manufacturers (MDR, Annex XIII)
Clinical evidence and corresponding Life Cycle phases

**Product Life Cycle**
- **Product Idea**
  - Feasibility Concepts
- **Strategic Decision**
  - Product Development
- **Product Launch**
  - Sales & Marketing

**Clinical Data**
- Preclinical Evaluation
- Clinical Evaluation or (Investigation)
- Postmarket Surveillance / PMCF Studies

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Manufacturer advantages through Clinical Evidence

**Early Collection & Evaluation of Clinical Data**
- by Scientific Literature
- through Clinical Experience
- with Clinical Investigations

**Clinical Evidence “opens doors”**
- Identification of missing Evidence
- Detection of potential Risks for Market Acceptance
- Clinical Risk/Benefit Assessment
- Estimation of Clinical Market Potential

**Strategic Decision on Product Development**
- Balancing of “best” Intended Use

**Definition of Approval Strategy**
- Clinical Evaluation based on Literature or Decision on Clinical Investigation?
- Postmarket Surveillance Study required?

**Additional Benefit of clinical evidence:**
- Competitive Advantage
- Early on Insight of potential Incidence
- Support for Marketing and specific Claims
- High Medical Benefit support Reimbursement
- Support of worldwide product approval

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Proposed Scrutiny Procedure (Article 44)  

Medical Device Directive Revision Proposal

Source: Eucomed’s response to the Commission’s proposal for the revision of the EU Medical Devices Directives, Position Paper, January 30, 2013

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Major Issues of the MDR still “under consideration”

- Scrutiny Procedure (Article 44)
- Delegation acts and Implementing acts:
  - more than 50 times throughout the MDR proposal
  - not in Line with Lisbon Agreement (Dec. 2007)
    without formal obligation to consult member states/stakeholders
- Clear Roles & Responsibilities of each ‘Economic Operator’
  (Manufacturer, Authorized Representative, Importer, Distributor)
- Harmonized Standards vs. Common Technical Specifications
- Notified Bodies
  (Competence?, Annual Assessments, transition period for manufacturer in case a NB gets de-notified)
- EU UDI legislation
  (not accepted by industry through a delegation act; industry readiness?; consistency with US/FDA- rules?)
- Extended Technical File will be needed
  (UDI, EUDAMED, for various economic operators)
- ‘qualified person’ responsible for regulatory compliance
  (within a manufacturer’s organization; scientific diploma + 5Y experience in Reg Aff. or QM)
Anticipated transitional „impact“ by MDR Regulation

MDR entry into force + 6 month + 3 years + 2 years

<table>
<thead>
<tr>
<th>NB</th>
<th>imm. actions</th>
<th>can apply for reassessment</th>
<th>must have been reassessed</th>
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<tbody>
<tr>
<td>Cert MDD/AIMD</td>
<td>valid</td>
<td>valid</td>
<td>valid</td>
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<tr>
<td>Cert MDD/AIMD</td>
<td>can apply</td>
<td>can apply</td>
<td>cannot any longer apply</td>
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<tr>
<td>Cert MDR</td>
<td>cannot apply</td>
<td>can apply and is valid</td>
<td>valid</td>
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<tr>
<td>Class I device</td>
<td>MDD</td>
<td>MDD/MDR</td>
<td>MDR</td>
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<td>Clinical investigations started before date of application</td>
<td>business as usual</td>
<td>business as usual</td>
<td>change SAE reporting</td>
</tr>
<tr>
<td>Clinical investigations according to MDR</td>
<td>not possible</td>
<td>possible</td>
<td>must be</td>
</tr>
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Source: Ralph Hilberath, BD
List of Harmonized Standards

<table>
<thead>
<tr>
<th>ESO (1)</th>
<th>Reference and title of the harmonised standard (and reference document)</th>
<th>First publication OJ</th>
<th>Reference of superseded standard</th>
<th>Date of cessation of presumption of conformity of superseded standard Note 1</th>
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Impact of the publication of EN ISO 14971:2012

The publication contains:

- The normative requirements as published in ISO 14971:2007
- It supersede the Annexes ZA, ZB, ZC as published in EN ISO 14971:2009
- The political impact is, that detailed table(s) are added, which Essential Requirements of MDD, IVD, AIMD are covered and which not.
- Therefore Requirements from the MDD supersede ISO 14971 in Europe:
  1. Treatment of negligible risks
  2. Discretionary power of manufacturers as to the acceptability of risks
  3. Risk reduction "as far as possible" versus "as low as reasonably practicable"
  4. Discretion as to whether a risk-benefit analysis needs to take place
  5. Discretion as to the risk control options/measures
  6. Deviation as to the first risk control option
  7. Information of the users influencing the residual risk
## Risk Acceptability

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<th>Probability of occurrence</th>
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### ALARP (As Low As Reasonable Practicable)

- **non-acceptable risk**
- **acceptable risk**
## Risk Acceptability - from Industry practice

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- **non-acceptable risk**
- **ALARP (As Low As Reasonable Practicable)**
- **acceptable risk**

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# Risk Acceptability - by EU-Commission

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- non-acceptable risk
- ALARP (As Low As Reasonable Practicable)
- acceptable risk
Risk Acceptability - a proposed compromise

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- non-acceptable risk
- **New: Medical Benefit vs. Residual Risk**
- As far as possible
Conclusion & Outlook

• 50% Chance that MDR / IVD will become new law in Europe (within the next 6 month)
• Clinical Evaluation / Investigation will become a mayor subject (including public database on clinical data)
• Qualification & Scrutiny of Notified Bodies will increase (Hidden goal: Decrease number of Notified Bodies by 50%)
• Chance fees & Payment Structure for Medical Device Approval (within the next 6 month)
• Increase transparency for Risk-Management & Clinical data (improve usability of Medical Devices)
• Introducing new rules for “Economic Operator” (Manufacturer, Authorized Representative, Importer, Distributor)