Update on Regulatory Environment - Europe

Experience with 2007/47/EC M5 & Discussions on Possible Recast of EU Medical Device Regulations

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Presentation to:

MassMEDIC
Agenda Topics

• Updated BSI overview
• Experience with 2007/47/EC
• Recast of MDD
• Changes to IVDD
• Other EU Issues
BSI Healthcare - Our Mission

To ensure patient safety while supporting timely access to medical device technology globally.

To provide our customers thorough, responsive, predictable conformity assessments, evaluations and certifications that are recognized and accepted worldwide.
BSI Healthcare Teamwork

- BSI Healthcare team of more than 200 people delivers world class expertise improving products, services and trading relationships globally.
- Doubled in size over last 3 years
- We help thousands of organizations to open new markets, maximize potential of existing markets and manage risk – making you more successful.

Healthcare Leadership Team Meeting  June 2010
2007/47/EC – M5 Experience
2007/47/EC M5 Focus

• Full force March 2010
  ▪ QMS auditing now
  ▪ Sampling technical documentation (new / changed ER’s)
  ▪ EC Design Examination Certificates confirmed on reissue

• Some non-EU manufacturers (not BSI customers) complaining that they never knew the change was coming

• Full compliance being achieved
2007/47/EC M5 Focus

• Essential Requirements
  ▪ Ergonomics (EN 62366)
  ▪ Biophysical modeling validity
  ▪ PPE & Machinery ER’s
  ▪ Clinical Evaluations
  ▪ Phthalates
  ▪ Software
  ▪ Labeling
    • Single use / re-use risk statement
2007/47/EC M5 Focus

- Updated Technical Documentation Sampling
  - Increased sampling according to MDD and NBOG Guidance
  - Define device subcategories / generic device groups
  - Preparation of sampling plans
  - Notified Body prepared rationale for technical documentation sampling plan
  - Changed ER’s / checklists

- Sampling more Technical Files, resulting in finding more problems and opportunities for improvement (particularly in IIa devices)
2007/47/EC M5 Focus

• Medicinal usefulness
  ▪ Improved documentation submitted to medicinal agencies, NB is required to submit their review to CAs, improve CAs timelines as result of M5 (as 210 days stated)

• Phthalates
  ▪ most manufacturer’s conforming, medical staff becoming more aware of devices containing phthalate, this change also is drawing attention to other CMRs that might leach

• Corrections of device classifications e.g., disinfectants for invasive devices and CNS

• EU Rep requirement clear resulting in consistency
Annex X - Clinical Evaluation

Assessment based upon

1. Compilation of relevant scientific literature and a written critical evaluation

2. The results of all clinical investigations and a written critical evaluation
Annex X – Clinical Evaluation

• The clinical evaluation and its outcome shall be documented. This documentation shall be included and/or fully referenced in the technical documentation of the device.

• The clinical evaluation and its documentation have to be actively updated with data obtained from the post market surveillance.

  ▪ Where post market clinical follow-up as part of the post market surveillance plan for the device is not deemed necessary, this must be duly justified and documented.
Clinical Evaluation – Not meeting MedDev 2.7.1 …

1. “Google” used to identify two or three papers, that are then summarised to demonstrate compliance.

2. Literature review includes ONLY published studies of mechanical testing, computer modelling, animal and *in vitro* experimentation.

3. Many papers identified, however not all selected for inclusion, without justification.

4. Devices described as “substantially equivalent.”

5. No discussion of differences or clinical risks of those differences between devices in published literature and device under review.
Clinical Evaluation – Not meeting MedDev 2.7.1 …

6. Equal reliance on clinical data from one multicentre randomised control trial and one expert opinion.

7. Reviewing the literature and finding your product has a new design feature, new indication or new material and not doing a clinical investigation.

8. Clinical Investigation – without notifying a EU Competent Authority or without any other regulatory authority approval.

9. Conclusion that the device under review is “substantially equivalent” to other devices in the published literature.

Post Market Surveillance (PMS)

• Some Member States seem concerned that PMS is not working and could be a part of next MDD revision or recast

• Common problems
  ▪ No PMS procedure
  ▪ No device / family specific PMS plan
  ▪ No Post Market Clinical Follow-up (PMCF)
    • No justification for no PMCF
Post Market Clinical Follow-up

• Recognize the limitations, desirability and value of pre-market data.

• Manufacturer’s quality system includes appropriate post market surveillance to learn from device use
  ▪ General PMS as well as defined PMS strategy for each of products/product range

• MEDDEV 2.12-2 PMCF
  ▪ Planned
  ▪ Service life of device
  ▪ Equivalency
  ▪ Post market clinical / registries etc.
EU MDD Annex II 3.2 - QMS

• Application of the quality system must ensure that the products conform to the provisions of this Directive which apply to them at every stage, from design to final inspection.

• Where the design, manufacture and/or final inspection and testing of the products, or elements thereof, is carried out by a third party, the methods of monitoring the efficient operation of the quality system and in particular the type and extent of control applied to the third party*.

*Introduced by 2007/47 M5
Renewals: Addressing New Regulatory Hurdles

Then

- Updated Legislation
- Updated MEDDEV Documents
- New Harmonised Standards
- State of the Art

Now
Areas to work on

• Notified Bodies:
  ▪ Technical file sampling rationales
  ▪ Annex V technical files sampling (without auditing design)
  ▪ QMS Auditing: PMS, Supplier Control,
Areas to work on

• Manufacturers:
  - Technical files updated
  - Clinical Evaluations
    - MED DEV 2.7.1 & GHTF SG5 N2R8
    - Procedure for Clinical and ‘active update’
  - PMS
    - MED DEV 2.12-1 & 2 and NB-MED 2.12
    - Do PMCF or document justification for no PMCF
  - QMS – supplier control
Areas to work on

• EC / Member States
  ▪ Manufacturers disappointed because standard for phthalates, guidance on risks of re-use, guidance on EHSR of machinery directive … not ready by 21/March implementation date.
    • Highly desirable and support consistency to have standards / guidance's prepared before implementation of requirements

• Manufacturers would like to have access to the EUDAMED (when operational).
  ▪ Actual data on devices already on the market can help to locate publications on similar devices, make decisions on probabilities of occurrence when assessing risks and help to determine sample sizes that will measure differences when planning clinical investigations.
No further breakdown on incidents possible.
No further breakdown on incidents possible.
Guidance from the centre

- MED DEV 2.7.1 Rev 3 (Dec 2009)
  - Clinical Evaluation: A Guide for Manufacturers and Notified Bodies
    (http://ec.europa.eu/consumers/sectors/medical-devices/files/meddev/2_7_1rev_3_en.pdf)

- MED DEV 2.4/1 Rev 9 (June 2010)
  - Classification of medical devices
    (http://ec.europa.eu/consumers/sectors/medical-devices/files/meddev/2_4_1_rev_9_classification_en.pdf)

- EU Commission Guidance Interpretive Documents:

- FDIS 14155 (draft) - Different from ISO 14155

- MHRA device specific guidance
EU Regulatory Recast - MDD
Recast needed?

• Discussions started in 2008
  ▪ 2007/47/EC was not yet fully implemented
  ▪ Consultation on several questions
  ▪ Possible involvement of EMA

• European Commission is concerned

• Some change / evolution seems inevitable

• Timetable
  ▪ Proposal by 2012
  ▪ Implementation 2015…
Areas of Concern

• Merge MDD & AIMD into one Directive
• Update IVDD
• Regulatory gap – devices incorporating human tissues / cells
• Designation & monitoring of Notified Bodies
  ▪ Evaluation of novel and highest risk devices
• Transparency
• Vigilance
Objectives for Recast

- High level of patient / user safety
- Responsive to innovation – speed to market, product life-cycle, iterative development of devices
- Need for competitive EU Med-Tech industry
- Increased transparency & trust

- EU healthcare systems need availability of competitive & alternative solutions for delivery of best achievable patient outcomes
Notified Bodies

• Harmonization of designation and monitoring
  ▪ Consistent conformity assessment / competence
  ▪ Group of 5 Notified bodies

• Role of Central Medical Device Committee / EMA

• Notified Body evaluation of highest risk devices
  ▪ Reference to another authority
  ▪ Harmonized evaluation criteria
  ▪ Access to clinical expertise
Other Recast Issues

• Vigilance / Post Market Surveillance
  ▪ Coordination of analysis of certain incidents and follow-up
  ▪ Cooperation between authorities

• Registration and Listing
  ▪ Central European databank (Eudamed)

• Improved coordination
  ▪ Medical Devices Committee
    • Secretariat (EMA / EC????)
Changes to IVDD
IVDD Timeline

- **Public Consultation**
  - Approx 3 mths
  - Finished Sep 10

- **Draft Proposal**
  - 3 mths
  - Finish Jan 2011

- **Interservices Consultation**
  - 15 working days
  - Finish Feb.

- **Alignment with the Recast**
  - Approx 3 mths
  - End Q2 2011

- **Commission Proposal**
  - Available early 2012

- **Discussion & adoption by EU legislator**
  - 15 - 31 months

- **Publication in OJEU**
  - 2013 - 2014

- **Transposition Period**
  - Approximately 18 months

- **Transition Period**
  - 6 - 12 months
Current Status

Public Consultation exercise closed on Sept 15th

What is the consultation?

• Preparative work for the first draft of the Directive
• Identifies issues and asks stakeholder opinions including
  ▪ Authorities,
  ▪ Users
  ▪ Industry
  ▪ Trade associations
• Considers the potential socio-economic data requested in public consultation
Classification

• IVDD currently has a list based classification
  ▪ Simple
  ▪ Not scientific or logical
  ▪ Rigid can’t accommodate new analytes e.g. vCJD

• Proposed change to a rules based system using GHTF model
  ▪ More complex to apply
  ▪ More scientific/ logical
  ▪ Flexible can accommodate new analytes
  ▪ More products will require a Notified Body or an approved QMS
# GHTF Classification

<table>
<thead>
<tr>
<th>CLASS</th>
<th>RISK LEVEL</th>
<th>EXAMPLES</th>
</tr>
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<tbody>
<tr>
<td><strong>A</strong></td>
<td>Low Individual Risk and Low Public Health Risk</td>
<td>Instruments, reagents e.g. prepared selective culture media specimen receptacles</td>
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</table>
| **B** | Moderate Individual Risk and/or Low Public Health Risk | Self test tests  
*All IVDs not in A, C or D e.g. Vitamin B12, POC, Urine test strips.* |
| **C** | High Individual Risk and/or Moderate Public Health Risk | Blood glucose self testing, HLA typing, PSA, screening, Rubella  
*STD, Cancer markers, cardiac markers, genetic tests* |
| **D** | High Individual Risk and High Public Health Risk | HIV Blood donor screening, HIV Blood diagnostic |

*Similar to general IVDs*  
*No IVDD equivalent*  
*Similar to Annex II list B*  
*Similar to Annex II list A*
Conformity Routes for IVDs

Risk

Higher

Pre market audit quality management system not required
Pre-market submission of technical documentation not required

Approved quality management system
Pre-market submission of technical documentation required

Or
Technical documentation sampling by NB

Approved quality management system
Pre-market submission of technical documentation required

Lower

Pre market audit quality management system not required
Pre-market submission of technical documentation not required

Approved quality management system
Pre-market submission of technical documentation required

Or
Technical documentation sampling by NB

Approved quality management system
Pre-market submission of technical documentation required

GHTF Classification

A

B

C

D
Impact of the changes

- The change in classification will increase the number of products requiring a Notified Body.
- The number of products which will be affected will depend on how the GHTF is applied.
- If applied as described in GHTF some self test devices may need less Notified Body involvement.
- Both companies and Notified Bodies will need to understand the impact of the changes.
- Companies need to understand the increased conformity assessment requirements.
- Notified Bodies need to ensure that they have the technical ability and resource to meet the need.
IVD Clarification

• In-house testing
  ▪ The amount of in-house testing conducted varies between member states, it can be on a large “industrial” scale and therefore raises concerns

• Genetic testing
  ▪ Scope of the IVDD could be expanded to include ALL genetic tests
  ▪ This would include paternity tests, tests determining future potential to develop diseases, life-style etc

• Diagnostic services
  ▪ Increasing number of labs providing tests directly to the public or physician and therefore not placing test on the market in the traditional way.
IVD Clarification

• Point of care
  ▪ Should POC tests meet the same requirements as self-tests IVDs, depending on the user of the test?
  ▪ Should the IFU identify the intended user e.g. Dr, nurse or trained healthcare assistant

• Companion diagnostics
  ▪ Should companion IVDs be risk assessed according to the side effects of the drug and severity of the disease in question?
Clinical Evidence

Clinical Validity
- Specifications
- Performance

Clinical Utility
Usefulness of the data to make a clinical diagnosis
Clinical Evidence

• General feeling amongst Competent Authorities that more clinical evidence will be required to support technical documentation

• Clinical Evidence documents currently at an early stage of development

• Acceptance that GHTF documents will be accepted to support European process
Clinical Evidence

• How much evidence will be required?

• Current thinking is that this should be commensurate with the risk of the device and the analyte i.e. could include spectrum from literature to studies

• Health economics is currently out of the scope
Conditional CE Marking

- Review will consider need for mechanism to address rare diseases or emergency situations such as a pandemic
- There needs to be rapid mechanism which can allow a rapid market access
- These devices would not need to meet all CE marking criteria but would be given a short term “conditional CE mark”
Other EU Issues
Reprocessing of SUD’s

- Report from the EC published August 2010
  - Problem quantifying risks associated with use of reprocessed devices
  - Clearly not all SUD’s are suitable for reprocessing
  - Evaluation and validation of whole process needed
- Inconsistency across EU Member States
EU Member States Concerns with ISO 13485

• EU Member States problem with 13485 is that they do not feel that it gives enough prominence to the areas where 2007/47 beefed up the Directives, in particular clinical data and post market experience:

  ▪ **7. Product realization** could be more specific about the necessity of clinical evaluation, including as a design input and/or as part of validation

  ▪ **8.2.1 Feedback** could be more specific about PMS
    • …there may be others…
Others

- E-labeling
- EUDAMED (2011)
- Animal tissue & TSE/BSE
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