Proposed Medical Device Regulation (MDR) & IVD Regulation (IVDR)

Overview of the Changes

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Caution

• The new regulations are not finalized and subject to change

• Further details will be added later pre and post application through Implementing and Delegated Acts

Background to the changes

- Discovery of a 16 year fraud in PIP breast implants using low quality “industrial grade” silicon oil
- Stress test performed by EU Commission
- Determine that changes were needed to improve early detection and prevent this type if incident
- Other high profile vigilance cases with hips, pelvic floor meshes, pacemaker leads, etc.

Outcome

- Short term changes proposed to the system:
  - Increased market surveillance
  - Additional unannounced visits on top of regular audits
  - Identify a person who is responsible for regulatory compliance
Three Directives become Two Regulations

• Impact of becoming a Regulation
• Direct entry into force
  • Three year transition period for MDD/AIMD
  • Three year transition period for IVD
• Regulation should result in more consistent application
• Appropriate legal instrument that imposes clear & detailed rules which become applicable in a uniform manner and at the same time throughout the EU
Timelines

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European Parliament 1ST Reading – October 2013

Finalise 1ST or 2nd Reading – Q4 2014 / Q1 2015

Designation of Notified Bodies

3 Year Transition

3 Year Transition

Regulation covering MD & AI MD

Regulation covering IVD
Delegated Entities under the Proposed Regulation

- European Commission (EC)
- EU Member States (MS)
- EU Competent Authorities (CA)
- Medical Device Coordination Group (MDCG)
  - Representatives of EU MS
- Medical Device Advisory Committee (MDAC)
  - Expert committee of stakeholders, provides advice to MDCG, MS, EC
  - Representatives from clinical experts, EMA and patients
- Assessment Committee for Medical Devices (ACMD)
- EU Reference Laboratories (EURL)
- European Medicines Agency (EMA)
- Notified Bodies (NB)
- Special Notified Bodies (SNB)
Role of Medical Device Coordination Group (MDCG)

• Contribute to the assessment of Notified Bodies
• Contribute to the scrutiny of certain conformity assessments
• Contribute to development of guidance, in particular:
  • designation and monitoring of Notified Bodies
  • application of the general safety and performance requirements
  • conduct of the clinical evaluation by manufacturers and the assessment by Notified Bodies
• Assist Competent Authority in the coordination of clinical performance studies, vigilance and market surveillance
• Provide advice and assistance to the Commission
Designation of Notified Bodies & Special NBs

Notified Body
MDR Class Ila/Iib**
IVDR Class B/C

Special Notified Body
MDR Class III/IIb**
IVDR Class D

No Notified Body
MDR Class I*
IVDR Class A

*Class I non-sterile / non-measuring
**Under MDR Special NB needed for higher risk devices: class III, implantable, devices intended to administer medicinal products
Notified Bodies

- More prescriptive requirements
  - Must have permanent in-house staff:
    - Administrative / Technical/Scientific / Medical / Pharmacological
  - May use External Experts on ad hoc and temporary basis as needed
  - Submission for designation of a Notified Body shall be overseen by three experts identified by the Commission and MDCG
  - Better defined Scopes of Designation relative to competence
- Only Special Notified Bodies can assess high risk devices / IVD’s
- Notified Body will apply to EMA to be designated as a Special Notified Body
  - Special Notified Bodies to meet in network, exchange good practice and convergence
  - In-house clinical experts
  - Two experts for each product category at least one in-house
Notified Bodies, Certificates and the Regulation

• Designations under AIMD, MDD and IVD become void at the date of final application of the regulation
• AIMD, MDD and IVD EC Certificates issued before the regulation enters into force remain valid until expiration date
• AIMD, MDD and IVD EC Certificates issued after the regulation enters into force shall become void two years after the application of the regulation
• Certificates against the new regulation can be issued by notified bodies designated under the new regulation before the date of application of the regulation
EU Medical Device Regulation (EU MDR)

- Combines, consolidates and replaces:
  - Active Implantable Medical Directive
  - Medical Device Directive
  - Reclassification of Breast Implants
  - Reclassification of Hip, Knee and Shoulder Joints
  - Animal tissue regulation

- 10 Chapters, 97 Articles and 15 Annexes
Structure of EU MDR

Ch I  - Scope & definitions
Ch II - Making available of devices, obligations of economic operators, reprocessing, CE marking, free movement
Ch III - Identification and registration of devices and economic operators, summary of safety and clinical performance, EU medical device databank
Ch IV - Notified bodies
Ch V  - Classification and conformity assessment
Ch VI - Clinical evaluation and clinical investigations
Ch VIa - Labeling and safe reprocessing of medical devices
Ch VII - Vigilance and market surveillance
Ch VIII - Cooperation between Member States, Medical Device Coordination Group, EU reference laboratories, device registries
Ch IX  - Confidentiality, funding, penalties
Ch X  - Final provisions
EU Medical Device Regulation: Annexes

- Annex I   - General Safety & Performance Requirements
- Annex II  - Technical Documentation
- Annex III - EC Declaration of Conformity
- Annex IV  - CE Marking of Conformity
- Annex V   - Information for Registration of Devices & Economic Operators & Data Elements UDI
- Annex VI  - Notified Body Requirements
- Annex VII - Classification Criteria Conformity Assessment Annexes
- Annex VIII - Full QA Plus Design Dossier Examination
- Annex IX  - Type Examination
- Annex X   - Product Conformity Verification
- Annex XI  - Conformity Assessment for Custom-Made Devices
- Annex XII - Content of Certificates Issued by a Notified Body
- Annex XIII - Clinical Evaluation and Post Market Clinical Follow-up
- Annex XIV - Clinical Investigations
- Annex XV  - List of Non-Medical Products Included in Medical Device Definition
Structure of the IVDR

Chapters 10
Articles 90
Annexes 14

Annex I General Safety and Performance Requirements
- Equivalent to the current essential requirement
- Broadly similar with additional clarification
- New sections for software and requirements for use with mobile platforms
- Requirements for self tests are extended to include near patient testing

Annex II Technical documentation
- Significantly more detail regarding the expectations for technical documentation

Annex III Declaration of Conformity
Annex IV CE marking
Annex V Registration and UDI
Annex VI Requirements for Notified Bodies
Annex VII Classification
Annex VIII Conformity Assessment based on Full QA or Design Examination
Annex IX Conformity Assessment based on Type Examination
Annex X Conformity Assessment based on Production QA
Annex XI Notified Bodies Certificate content
Annex XII Clinical Evidence and Post Market Follow up
Annex XIII Interventional Clinical Performance Studies
Annex XIV Correlation table

More detailed consistent with the proposed Medical Device Regulation
Medical Device

‘medical device’ means any instrument, apparatus, appliance, software, implant, reagent, material or other article, intended by the manufacturer to be used, alone or in combination, for human beings for one or more of the specific direct or indirect medical purposes of:
• diagnosis, prevention, monitoring, prediction, treatment or alleviation of disease,
• diagnosis, monitoring, treatment, alleviation of or compensation for an injury or disability,
• investigation, replacement or modification of the anatomy or of a physiological process or state,
• control or support of conception,
• disinfection or sterilisation of any of the above-mentioned products,
• providing information concerning direct or indirect impacts on health
and which does not achieve its principal intended action by pharmacological, immunological or metabolic means, in or on the human body, but which may be assisted in its function by such means.

The implantable or other invasive products, intended to be used for human beings, which are listed in Annex XV shall be considered medical devices, regardless of whether or not they are intended by the manufacturer to be used for a medical purpose.
'in vitro diagnostic medical device' means any medical device which is a reagent, reagent product, calibrator, control material, kit, instrument, apparatus, equipment, software or system, whether used alone or in combination, intended by the manufacturer to be used *in vitro* for the examination of specimens, including blood and tissue donations, derived from the human body, solely or principally for the purpose of providing information:

- concerning a physiological or pathological state;
- concerning a *physical or mental impairments*;

*In vitro diagnostic medical devices used for DNA-testing shall be subject to this Regulation*

- concerning the predisposition to a medical condition or a disease;
- to determine the safety and compatibility with potential recipients;
- to predict treatment response or reactions;
- to define or monitor therapeutic measures.
Definitions

- **Medical Device**
- **Accessory**
- **Label**
- **Instructions for use / Unique Device Identification**
- **Manufacturer / Authorized Representative / Importer / Distributor / Economic Operator**
- **Health Institution / User / Lay Person**
- **Reprocessing / Fully Refurbishing**
- Conformity assessment terms
- Clinical terms
- Vigilance and market surveillance terms
Single-Use Devices

• *Single-use device* – ‘...has been tested and demonstrated impossible to reuse.’
• Devices labeled as single-use should really be single-use
• *All devices should be reusable as a rule, unless they are on a list established by the EC after consultation with MDAC*
• *Reusable device* – ‘..suitable for reprocessing’ for multiple patients/procedures
Economic Operators

Manufacturer

means the natural or legal person who manufactures or fully refurbishes a device or has a device designed, manufactured or fully refurbished, and markets that device under his name or trademark

Importer

means any natural or legal person established within the Union who places a device from a third country on the Union market

Distributor

means any natural or legal person in the supply chain, other than the manufacturer or the importer, who makes a device available on the market

Economic operators

means the manufacturer, the authorised representative, the importer and the distributor
Increased Control of the Supply Chain

- Crucial Suppliers
- OEM’s
- Sub contractors
- Distributers
- Importers
- Authorised Representatives

Manufacturer
Increased Control of the Supply Chain

- Increase expectation to hold or have quick access to technical documentation during audits
- Notified bodies can now audit crucial suppliers as well as significant subcontractors including unannounced visits
- Changes to contracts will be required
General Obligations of Manufacturer

- Design and manufacture devices in accordance with the regulation
- Draw up required technical documentation
- Complete an appropriate conformity assessment
- Prepare a declaration of conformity
- Make technical documentation available to CA’s (STED)
- Operate a quality management system and maintain product conformity
- Conduct post market surveillance
- Supply adequate instructions for use in a MS language
- Procedures for devices that do not comply – including vigilance
- Identify suppliers conducting device design, manufacture
- Liability insurance
Obligations of Authorized Representative, Importers, Distributors

- Manufacturer designates by written mandate a single authorized representative confirmed in writing by the authorized representative
- Prescriptive requirements for authorized representative
- Written process for changing authorized representative
- General obligations of importers
  - Confirm: **manufacturer identifiable and competent, liability insurance, conformity assessment, authorized representative, technical documentation, devices CE Marked, labeled in accordance with regulation**
  - Identify themselves, registration, storage & transportation, records, complaints, non-conformity/corrective action responsibilities
Eudamed: European Electronic Database

- UDI
- Registration of devices and economic operators
- Information of certificates
- Clinical investigations
- Vigilance
- Market surveillance
- Public access
  - Allow comparison of devices, economic operators, clinical investigations, vigilance
Traceability in the Supply Chain

- For devices, other than devices for clinical investigation or performance evaluation, economic operators shall be able to identify the following, and will retain records for the 5 years after the last device has been placed on the market:
  (a) any economic operator to whom they have supplied a device;
  (b) any economic operator who has supplied them with a device;
  (c) any health institution or healthcare professional to whom they have supplied a device.

Unique Device Identification (UDI)

- To facilitate traceability and recall devices will require a UDI
- Does not apply to devices for clinical investigation / performance evaluation
- The UDI will appear on the label
- Will need to be stored by the economic operators and the health institutions
- Approved systems will be designated by the Commission
  - Coherent if possible with a global regulatory approach to UDI
Person Responsible for Regulatory Compliance

- Manufacturers within their organisation at least one qualified person who possesses expert knowledge in the field of in vitro diagnostic or medical devices. This will include:
  - a degree or equivalent in natural sciences, medicine, pharmacy, engineering, law plus at least two years of professional experience in regulatory affairs or in QMS in medical devices or IVD's or
  - Three years of professional experience in regulatory affairs or in QMS relating to medical devices or IVD's

- Responsible for ensuring:
  - that the conformity of the devices is appropriately assessed before a batch is released
  - that the technical documentation and the declaration of conformity are drawn up and kept up-to-date
  - that vigilance requirements have been fulfilled
  - Subjects in clinical investigations or performance evaluation for interventional studies

- The qualified person should suffer no disadvantage by performing their duties
- Authorised representatives will also be required to have person responsible for regulatory compliance
Classification Changes

- **MDR classification changes**
  - Brings AIMD and accessories are class III
  - Identifies spinal disk replacement implants and implantable devices that contact the spinal column are class III
  - Devices incorporating nanomaterial deliberately intended to be released to the human body are class III
  - Sutures and staples used in direct contact with CCS/CNS are not class III
  - Devices intended for aphaeresis are class III
  - Devices intended to be ingested, inhaled or administered rectally or vaginally and are wholly or partially absorbed by or dispersed in the human body are class III
1.1. Application of the classification rules shall be governed by the intended purpose, *novelty, complexity and inherent risk* of the devices.
Classification

**Class D (Blood screening)**

- Devices intended to be used to detect the presence of, or exposure to,
  - a transmissible agent in blood, blood components, cells, tissues or organs, or in any of their derivatives, in order to assess their suitability for transfusion or transplantation.
  - a transmissible agent that causes a life-threatening disease with a high or currently undefined risk of propagation
- Blood grouping ABO, Rhesus, Kell, Kidd and Duffy systems

**Class C**

Devices intended for

- detecting the presence of, or exposure to, a sexually transmitted agent;
- detecting the presence in cerebrospinal fluid or blood of an infectious agent with a risk of limited propagation;
- detecting the presence of an infectious agent, if there is a significant risk that an erroneous result would cause death or severe disability to the individual, foetus or embryo being tested, or to the individual's offspring;
- pre-natal screening of women in order to determine their immune status towards transmissible agents;
- determining infective disease status or immune status, if there is a risk that an erroneous result would lead to a patient management decision resulting in an imminent life-threatening situation for the patient or for the patient's offspring;
**Classification**

**Class C (Continued)**

- selection of patients, *i.e.*
  - Devices intended to be used as companion diagnostics*; or
  - Devices intended to be used for disease staging *or prognosis*;
  - Devices intended to be used in screening for or in the diagnosis of cancer.
- human genetic testing;
- monitoring of levels of medicinal products, substances or biological components, when there is a risk that an erroneous result will lead to a patient management decision resulting in an imminent life-threatening situation for the patient or for the patient's offspring;
- management of patients suffering from a life-threatening infectious disease;
- screening for congenital disorders in the foetus *or embryo*
- Devices intended for self-testing are classified as class C, except those devices from which the result is not determining a medically critical status, or is preliminary and requires follow-up with the appropriate laboratory test in which case they are Class B.
- devices intended for blood gases and blood glucose determinations for near patient testing* are class C. Other devices that are intended for near-patient testing shall be classified in their own right.

*Companion diagnostic means a device specifically intended for and essential to the selection of patients with a previously diagnosed condition or predisposition as suitable or unsuitable for a specific therapy with a medicinal product or a range of medicinal products.*
Genetic Tests

‘device for genetic testing’ means an in vitro diagnostic medical device the purpose of which is to identify a genetic characteristic of a person which is inherited or acquired during prenatal development;

New requirement
The following devices may only be supplied on a medical prescription:

1) Class D devices;
2) Class C devices in the following categories:
   (a) devices for genetic testing;
   (b) companion diagnostics.
Classification

Class B
• Any IVD not listed under Classes D, C or A.
• Controls without an assigned value.

Class A
• Reagents, other articles with specific characteristics.
• Instruments intended specifically for use in IVD procedures.
• Specimen receptacles.
Note Class D devices regardless of whether they are used in a single healthcare institution must meet the regulation with the exception of the requirements for economic operators unless there is no CE marked device. Class A, B + C devices used within a single healthcare institution which have a single quality management system compliant with ISO 15189 (Medical laboratories - Particular requirements for quality and competence) may be exempt from the majority of the regulation; however, they must report adverse incidents.
Quantum Leap

**IVD Directive**
- Require a Notified Body
- Do not require a Notified Body
  - 80-90%

**IVD Regulation**
- Require a Notified Body
  - 80-90%
- Do not require a Notified Body
CE marking of conformity

• New requirement – when CE Marking is used in promotional material the notified body number must also be identified

• The form of CE Marking “CE Medical Device”
Declaration of Conformity Content

- Manufacturer name and address
- Statement that the manufacturer is taking responsibility for the device
- UDI device identifier
- Device identification – name, product code, catalog,
- Statement of compliance with the regulation
- Risk classification
- Harmonized standards used for conformity
- Notified body, conformity assessment, certificate
- Place, date of issue
- Name and function of signature, indication of who on behalf of signs
- Continuously updated and issued in one of the official EU languages
Conformity Assessment - MDR

• Annex VIII Full Quality Assurance
• Introduction of a minimum frequency for unannounced visits (taking account of device risks / types)
• Tests to be carried out by notified bodies – sample checks
• Notified body shall rotate the members of the audit team (no more than three years per lead auditor)
Safety and Clinical Performance Report

• For all class III and implantable device
• Based on data collected during the clinical investigation
• Submitted to Special Notified Body for review
• Special Notified Body will validate
• Must be understandable by users in the relevant local MS language
• The summary will be made available to the public through Eudamed
• Safety and clinical performance report shall be updated annually with clinical evaluation reports
Special Notified Body Assessment of High Risk Devices

- Only Special Notified Bodies shall conduct conformity assessment of high risk devices
  - MDR class III, implantable, class IIb intended to administer medicinal substance
  - IVDR class D
- Special Notified Bodies are designated by EMA
- All applications for high risk devices shall be notified to the EC
  - Notification will include
    - Draft IFU
    - Draft summary of safety and clinical performance
    - Estimated date of completion of conformity assessment
  - Notification will be communicated to MDCG
  - Within 20 days MDCG may request prior to CE Marking SNB provide (Under IVDR triggered by three members of ACMD)
    - Clinical evaluation report (IVDR clinical evidence / clinical performance study)
    - Post Market Clinical Follow-up Plan
    - Information on marketing or not in third countries (results of evaluations)
Special Notified Body Assessment of High Risk Devices (continued)

- MDCG will consult ACMD
- At the latest of 60 days MDCG will issue opinion on documents submitted
  - Within that period <30 days ACMD may request additional information
- Within 15 days of receiving MDCG opinion SNB will indicate whether it agrees
- If SNB disagrees it has 30 days to submit further information and request re-examination
- MDCG in consultation with ACMD has a further 30 days to re-examine opinion
- Following unfavorable opinion SNB shall not issue a certificate
- SNB can submit new information and MDCG may reassess application
- Following unfavorable opinion manufacturer can request from EC a hearing to discuss the scientific grounds for the unfavorable scientific assessment
- The EC will make MDCG opinions available to the public
- The manufacturer will not be charged for the additional MDCG assessment
Additional Requirements for Class D Devices

Greatest impact on devices which have been up classified or novel devices not included in a CTS

Summary of safety and performance
High risk devices (Class C and D) devices will require a summary of safety and performance which will be available to the public and should be is clear to the intended user.

Maximum 175 days
Parts and Components

• New requirement for suppliers of parts or components
  • Parts or components intended to replace parts or components that are defective or worn to maintain or re-establish performance of a device
• Responsibility to determine the part or component does not adversely affect the safety and performance of the device
  • Substantiating evidence available to CA’s
• For implantable devices must cooperate with the manufacturer of the device
• Part or component that significantly changes the performance or safety characteristics of a device shall be considered a device in its own right.
Implant Card and Information about Implantable Devices

- Manufacturers of implantable devices shall provide implant card for particular patients
  - Implant card shall also be made available in an electronic format
  - Identifies device implanted including UDI
  - Warning, precautions, measures to be taken with reciprocal interference with external influences (e.g. compatibility with diagnostic devices)
  - Potential adverse effects
  - Information on expected life cycle and follow-up
  - Principal characteristics of device including materials
- Exempted implants: sutures, staples, dental implants, screws, plates
Clinical Evaluation & Clinical Investigation - MDR

• Regulation combines and incorporates current guidance's on clinical evaluation and clinical investigation
• Significant requirements on clinical
  • General requirements – sponsor responsibilities
  • Application
  • Registration
  • Electronic system
  • Post market clinical investigation requirements
  • Substantial modification
  • Sponsor information obligations regarding suspension / termination
  • Event reporting
Clinical Requirements IVD

- Increased expectation for clinical requirements
- Clinical evidence is to be kept up to date during the life time of the device

The GHTF documents now in the IMDRF archive best guidance
- Clinical Performance Studies for In Vitro Diagnostic Medical Devices
- Clinical Evidence for IVD Medical Devices – Key Definitions and Concepts
- Clinical Evidence for IVD Medical Devices – Scientific Validity Determination and Performance Evaluation

Diagram showing the relationship between Clinical Evidence, Analytical Performance, Scientific Validity, and Clinical Utility.
Common Technical Specification (CTS)

- CTS may be written where no Harmonised Standards exist to address
  - General safety and performance requirements
  - Technical documentation
  - Clinical evidence and post-market follow-up
- Devices which are in conformity with the CTS shall be presumed to be in conformity with the requirements of the Regulation
- Manufacturers shall comply with the CTS unless they can duly justify that they have adopted solutions ensuring a level of safety and performance that is at least equivalent
Post Market Requirements

• Increased requirements for Post Market Surveillance
  • The post-market surveillance plan including
  • the process for collecting, recording and investigating complaints and reportable incidents,
  • keeping a register of non conforming products and product recalls or withdrawals,
  • if deemed appropriate sample testing of marketed devices
• Where post-market follow-up is not necessary, this has to be duly justified and documented in the post-market surveillance plan
• There is a provision to create registries for certain devices to gain post market information
Vigilance & Market Surveillance

• Regulation combines and incorporates current vigilance guidelines
  • Electronic system

• Member State market surveillance activities
  • Procedures for problem / non-compliant devices uniformly
  • Action against economic operators
Any Questions

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