What you need to know about the new European IVD Regulation

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September 2014
What you need to know about the new European IVD Regulation

• What is it?
• Why do we need it?
• When is it coming?
• What are the major changes?
  • Risk-based IVD Device Classification Approach
  • Routes to Conformity
  • Clinical Expectations
  • Responsibilities of the Manufacturer, Importer and Distributors and In-house Manufacture
Caution

• The new regulations are draft and subject to change

• Further details will be added later pre and post application through implementing and delegating legislation
BE CAREFUL
FASTEN SEAT BELT
ROUGH ROAD
Why do we need it?
Impetus for 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
STEP CHANGE 2016-2018

2010 - 2018

Guidance and interpretation

Then

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

Now

Joint audits
CoC audits
UAV
COEN - MS

Requirements and Transparency

MDR / IVDR
Clinical trials
EU oversight
Special NBs
EUDAMED
UDI
Electronic submission
Industry in Spotlight
and MORE....

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Advantages to the proposed changes

- Appropriate regulation of the entire IVD market
  - Current directive focuses on a limited number of devices of particular concern at the time of issue
  - New risk-based classification scheme captures the majority of devices, and is applicable to new devices that may come to market in the future
  - The level of regulatory scrutiny is commensurate with the relative risk of the device

- Consistent application
  - Under the current directive, each member state has implemented the directive slightly differently into national law
  - Raises concern about unequal competition
Notified Body Code of Conduct

• Mandatory to sign for TEAM-NB members
• Available on website www.team-nb.org

• New version to be approved on paper soon
  • Frequency of UAV
  • Focus of UAV
What is it?
IVD directive will become a regulation

What’s the difference

• A Directive is agreed by the European Parliament and Council and directs member states to pass national legislation to implement the directive
• A Regulation is a law agreed by the European Parliament and Council that takes effect directly in all member states

Impact of becoming a regulation

• The regulation is intended to result in more consistent application
  • The same text is in force in all member states
• Direct entry into force
• No Transposition period
  • No need for transposition into national law
• There will be a transition period of 3 years - reduced from 5 in the first draft
• The reduction to 3 years is intended to align with the MDR
• The regulation identifies areas which can be updated in the future using additional implementing acts according to Article 84(3)
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 & more prescriptive; consistent with the proposed Medical Device Regulation
When is it coming?
Timeline

ENVI
Parliament approved the ENVI report

Plenary Vote

Council
Second Reading

Adoption

Implementing Acts

Transition

Enforced

IVDR 2015-6

3 Years possibly 5 years

IVDR must be applied 2018-20
Managing the transition

Entry into Force

- NB designation (6 months)
- Implementing measures (12 months)
- Cooperation Between Authorities (12 months)
- Unique Device Identification Systems (UDI) (18 months)
- New Vigilance Procedures (24 months)
- New conformity assessment procedures, including use of clinical evidence (24 months)
Timeline

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IVDR must be applied 2018-20
What are the major changes?
Risk-based classification approach
Change to scope of IVDR through MDR

- ‘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, prognosis**, 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,
  - investigation, replacement or modification of the anatomy or of a physiological process or state,
  - 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 intended function by such means.

**Impact**
Tests to predict the likelihood patients will develop cancer or heart disease will be included, Life style tests for example tests to suggest dietary changes for health reasons will be included
Scope

‘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;
- 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.

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

Classification
Classification Exercise

- In your groups, classify the IVD products on your assigned cards according to the proposed IVD Regulation
- Use the classification flow chart and the classification rules in Annex VII (see the handout)
- Record the classification and the applicable rule on the worksheet

30 minutes
Click here to start
Routes to conformity
Conformity Assessment Routes

A
EC Declaration of Conformity Annex III

B
Full Quality Assurance Annex VIII*

C
- Full Quality Assurance Annex VIII*
  - Type Examination Annex IX
    - Production Quality Assurance X
      - For Companion Diagnostics CA Consultation

D
- Full Quality Assurance Annex VIII*
  - Type Examination Annex IX
    - Design Dossier including CTS
      - Production Quality Assurance X
    - Batch Verification

Note
In addition, Self Tests also have to meet the requirements in Annex VIII.6
Designation of Notified Bodies and Special NBs

- No Notified Body Class A
- Notified Body Class B & Class C
- Special Notified Body Class D
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
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
Clinical Expectations
Clinical Requirements

- 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
Elements of Clinical Evidence

**Scientific Validity**
refers to the association of an analyte to a clinical condition or physiological state

For established analytes, this may be from the literature; but for companion diagnostics or novel analytes this needs to be established

**Analytical Performance**
refers to the ability of an IVD medical device to correctly detect or measure a particular analyte

Sensitivity/specificity similar to current essential requirements

**Clinical Performance**
refers to its ability to yield results that relate to a particular clinical condition/physiological state for the intended use and in accordance with target population and, where applicable, the intended user

Data to support reference ranges etc.
Clinical Utility

The usefulness of the results obtained from testing with the IVD medical device and the value of the information to the individual being tested and/or the broader population

- Clinical Utility has never been a regulatory requirement in Europe
- Clinical Utility is still under discussion but likely to be required for companion diagnostics, according to the proposed amendment
Responsibilities of the manufacturer, importer and distributors plus in-house manufacture
Economic Operators

Manufacturer
means the natural or legal person with responsibility for the design, manufacture, packaging and labelling of a device before it is placed on the market under that person's own name, regardless of whether those operations are carried out by that person or on that person's behalf by a third party. The obligations of this Regulation to be met by manufactures also apply to natural or legal persons who assemble, package, process, fully refurbish or label one or more ready-made products and/or assign to them their intended purpose as devices with a view to their being placed on the market under that person's own 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;
Control of the Supply Chain

• Increase expectation for virtual manufacturers and OBL 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
Increased Control of the Supply Chain

- Regulatory roles and requirements of
  - Importers
  - Distributers
  - Authorised Representatives

These include
- Registration and keeping data up to date
- Mandate with the authorised representative
- Roles in vigilance and recall
- Required to have a Person responsible for regulatory compliance
- Manufacturers now have to have liability insurance but importers required to check this is adequate or take out their own
Person Responsible for Regulatory Compliance

- Manufacturers shall have available within their organisation at least one person responsible for regulatory compliance who possesses the requisite expertise in the field of in vitro diagnostic medical devices.

- This will include:
  - a degree or equivalent in natural sciences, medicine, pharmacy, engineering or law
  - or 3 years of professional experience in regulatory affairs or in QMS relating to IVDs

- The person responsible for regulatory compliance is 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.
  - for performance evaluation for interventional studies

- If compliance is shared between more than one person, responsibilities will be defined in writing

- This person should suffer no disadvantage by performing their role

- Authorised representatives will also be required to have a person responsible for regulatory compliance within their organisation.
Health Institution Definition

• means an organisation whose primary purpose is the care or treatment of patients *and which has the legal capacity to carry out such activities*;

• *commercial laboratories which provide diagnostic services shall not be considered to be health institutions*;
In-house Exemption for Class D IVDs

- If Class D devices are manufactured and used within a single health institution, they are exempt from the requirements of this Regulation, with the exception of vigilance requirements and general safety performance requirements where the following conditions are met:
  - (a) the recipient patient or patient group’s specific needs cannot be met by an available CE-marked device as such, and therefore, either a CE-marked device needs to be modified or a new device needs to be manufactured;
  - (b) the health institution is accredited to ISO standard 15189 quality management system, or any other equivalent recognised standard;

- The Commission shall verify that the devices on that list are eligible for exemption in accordance with the requirements under this paragraph.
- The information on exempt devices shall be made public.
- Member States shall retain the right to restrict the in-house manufacture and use of any specific type of in-vitro diagnostic device in relation to aspects that are not covered by this Regulation, and may also make the manufacture and use of the devices concerned subject to further safety requirements. In such cases, Member States shall inform the Commission and the other Member States accordingly.
Conformity Assessment Routes

**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.
Emerging Pathogens

• *In the case of urgent or unmet medical needs for patients, such as emerging pathogens and rare diseases, single health institutions should have the possibility of manufacturing, modifying and using devices in-house and thereby addressing, within a non-commercial and flexible framework, specific needs which cannot be met by an available CE-marked device.*

• *However, devices which are manufactured within non-health-institution laboratories and put into service without being placed onto the market should be subject to this Regulation.*
**EUDAMED**

**European Databank on Medical Devices**
(as proposed by the European Commission)

- **Electronic system on Registration**
  - Medical devices / IVDs economic operators, incl. Summary of Safety and Clinical Performance (high risk devices)

- **Electronic system on UDI**
  - Device Identifier data elements

- **Electronic system on Certificates**
  - Certificates issued by notified bodies & Information on certificates refused suspended reinstated restricted withdrawn

- **Electronic system on Vigilance**
  - Serious incidents & Field safety corrective actions & Field safety notices

- **Electronic system on Market surveillance**
  - Measures taken by Member States re. devices presenting a risk to health & safety preventive health protection measures

- **Electronic system on Clinical investigations**
  - Sponsors (& manufacturers) description of: investigational device, comparator, purpose of CI, status of CI
UDI

Bar-coding for every Medical Device

UDID Database
For DI part Only

DI
- Company Name
- Address
- Product Name
- GMDN code
- term
. etc

PI
Production Information
- Life
- Serial or Lot Information

DI
Device Information
- Company
- Product ID
Unique Device Identifier

- The Commission shall be empowered to adopt delegated acts in accordance with Article 85:
  - (a) determining the devices, categories or groups of devices, whose identification shall be based on the UDI system, ... and the timelines for implementing this. Following a risk-based approach, implementation of the UDI system shall be gradual, starting with devices falling in the highest risk class;
  - (b) specifying the data to be included in the production identifier which, following a risk-based approach, may vary depending on the risk class of the device;
  - (c) defining the obligations of economic operators, of health institutions and of professional users, in particular regarding allocation of the numeric or alphanumeric characters, placement of the UDI on the label, storage of information in the electronic system on UDI, and use of the UDI in documentation and reporting related to the device provided for in this Regulation;
  - (d) amending or supplementing the list of information ... in the light of technical progress.

- UDI will ultimately be required
  - Development of a UDI system is lagging behind US efforts
  - The European Commission intends to make the system as similar as possible to the US system.
  - For the time being, following US rules should prepare manufacturers adequately for European roll-out
Final Summary

- This is happening
- There is no grandfathering
- Requirements and expectations are increasing
- Keep up to speed and understand the impact to your organisation
- Talk to your notified body about their plans for designation and resource
- Classify your devices
- Look at the clinical data you have,
  - is it enough?
  How can you get what you need?
- Discuss at management reviews
Exercise 2:

Preparation for the IVDR
Instructions

• In your teams make a list of items to be considered when planning a strategy for implementing the IVDR
• Are there any dependencies?
• What order would you put them in?