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Changes to the Regulation of IVDs in Europe

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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

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Why?

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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

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What?

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IVDD will become a regulation

Impact of becoming a regulation

- Direct entry into force
- No Transposition period
  - No need for transposition into national law
- There will be a transition period 3 years reduced from 5 in the first draft
- There has been some discussion to reduce this to 3 years in line with the MDR
- A regulation should result in more consistent application
- The regulation identifies areas which can be updated in the future using additional implementing acts according to Article 84(3)

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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

When?

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EU Process

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Trialogue – Parties Trying to Reach Agreement

- European Commission
  - Prepared proposal 26 Sep 2012
  - *New Commissioner in Sep 2014*
- European Parliament – representing the citizens of Europe
  - Committees working on counter proposals
  - IMCO (113 IVD and 212 MDR amendment proposals), voting done
  - EMPL (20 IVD and 60 MDR amendment proposals), voting done
  - ENVI (399 IVD and 907 MDR amendment proposals), voting done
  - *First reading full Parliament – 22 October 2013 – open vote*
  - *Full Parliamentary vote 2 April*
  - *Re-elections May 2014*
- European Council of Ministers – representing EU Member States
  - *Just completed first read through Com proposal*
  - *Plan to complete counter proposals before July 2014*

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Timeline

IVDR 2014-2015
likely 2015

3 Years

IVDR must be applied 2018

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Classification and Conformity

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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

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IVD Classification

1.1. Application of the classification rules shall be governed by the intended purpose***, novelty, complexity and inherent risk*** of the devices.

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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;

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Classification

*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;

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.

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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.

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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.

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Conformity Assessment Routes

Self Tests also have to meet the requirements in Annex VIII.6

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.

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Designation of Notified Bodies and Special NBs

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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

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Quantum Leap

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Clinical Expectations

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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

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Elements of Clinical Evidence

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.

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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

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Responsibilities of the manufacturer, importer and distributers plus in-house manufacture

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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

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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

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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 share 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.

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COMMISSION IMPLEMENTING REGULATION (EU)

No 920/2013

of 24 September 2013

on the designation and the supervision of notified bodies under Council Directive 90/385/EEC on active implantable medical devices and Council Directive 93/42/EEC on medical devices

Directs Competent Authorities how to control Notified Bodies

COMMISSION RECOMMENDATION

of 24 September 2013

on the audits and assessments performed by notified bodies in the field of medical devices

Directs Notified Bodies how to audit manufacturers

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Commission Recommendation on the audits and assessments performed by NBs

Annex I

- Criteria for NBs performing design dossier and type examinations

Annex II

- Criteria for NBs performing QMS assessments

Annex III

- Unannounced visits to manufacturers "critical subcontractor" or “crucial suppliers”

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Unannounced Audits **HAS STARTED!!**

- Conducted at least once every third year, once every two years for high risk devices annually for non-compliant devices or of their manufacturer.
- Truly unpredictable.
- One day and should be executed by at least two auditors.
- Notified bodies may visit premises of critical subcontractors or crucial suppliers.
- Notified bodies should check a recently produced adequate sample for conformity with the technical documentation
- File review and a test could be "witness testing"
- The review should include verification of traceability of all critical components
- Manufacturers will have to pay for the visits, travel, testing and security for the assessment team is required
- If visa's are required to visit any sites, subcontractors or crucial suppliers then an open invitation letter will be included in the contract

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Preparation for unannounced visits

- Read the recommendation
- Budget for the cost
- Prepare a procedure for managing unannounced visits
- Define responsibilities in the event of an unannounced visits with backups/ emergency contacts
- Define critical sub contractors and crucial suppliers
- Review contracts with sub contractors and crucial suppliers
- Communicate with all staff including reception
- Explain this is mandatory and impact to certification if they refuse
- Practice

Note this applies if you have a Notified Body i.e. for Annex II List A + B and self test under Annex IV but not III.6. It does not apply if products are self designated under Annex III even if you have ISO 13485

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Final Summary

- 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
- Follow the negotiations

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