Changes to the IVD Regulations in Europe: What, When, Hot Topics and Areas of Uncertainty

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Caution

- This is a proposals for the new regulations and subject to change
- Some proposed elements are more concrete than others
- Further details will be added later pre and post application through implementing and delegating legislation

What?

IVDD will become a regulation

Impact of becoming a regulation

- Direct entry into force
- No Transposition period
  - i.e. no transposition into national law
  - There will be a transition period this is 5 years in the draft but there has been some discussion to reduce this to 3 years in line with the MDD
- 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)

Structure of the IVDR

The regulation is significantly longer, more detailed, more prescriptive

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

Structure of the IVDR

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 FQA 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

Note
The numbering will be in line with Medical Device regulation

When?

Approximate dates for the IVD

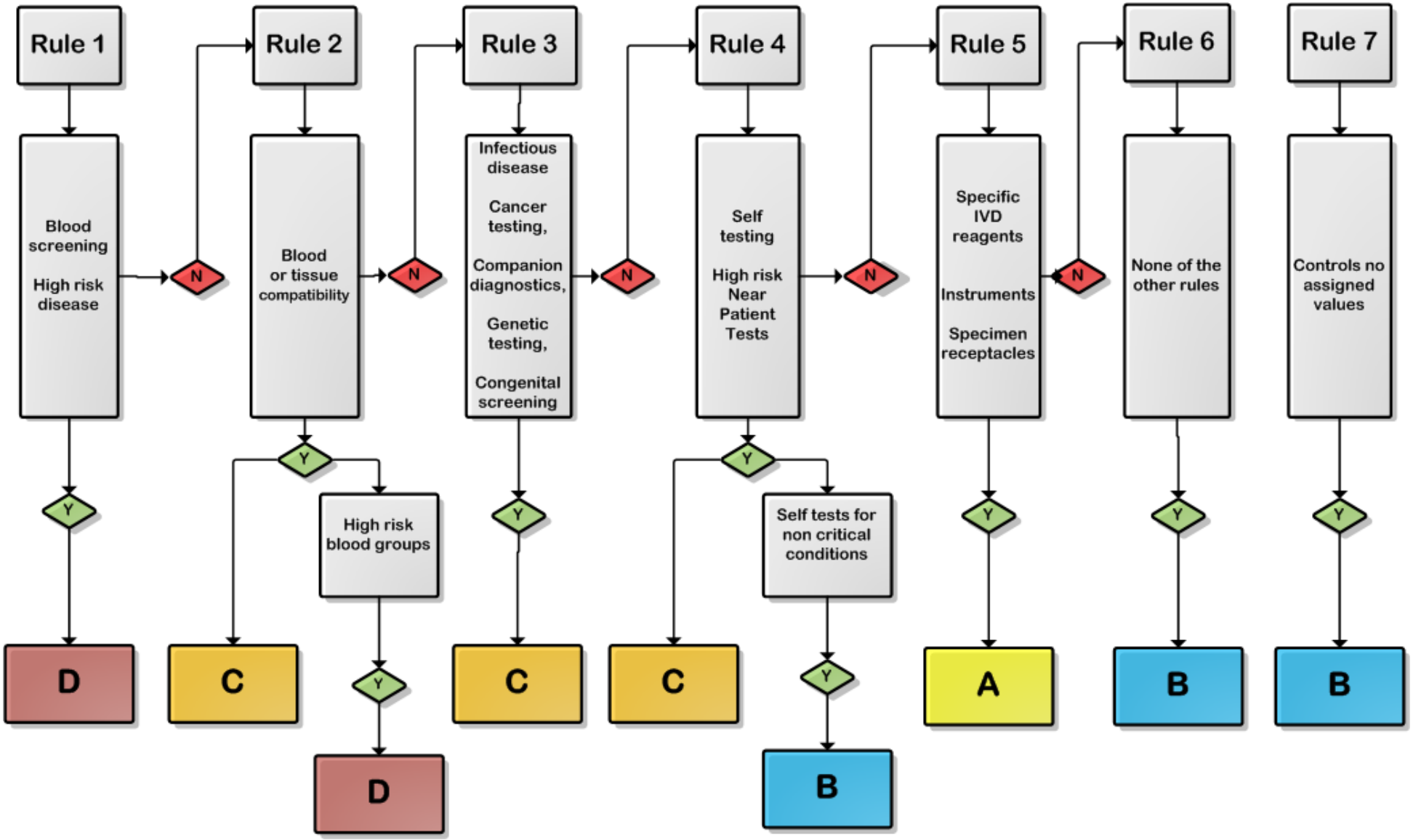
ID	2012	2013				2014				2015				2016				2017				2018				2019				2020			
	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
1	Publication of the proposal																																
2	EU Parliament 1st Reading																																
3						EU Parliament 2nd Reading																												
4														Designation of NBs																			
5																		Application				Transition								Entry in to Force			

Initial proposal for a 5year transition but there has been some debate as to whether this should be shortened to 3 years in line with the Medical device regulation

Hot Topics?

Classification and Conformity

IVD Classification



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 or foetus, 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
  - 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
- 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 to select patients with a previously diagnosed condition or predisposition as eligible for a targeted therapy

*Device for near-patient testing
means any device that is not intended for self-testing but is intended to perform testing outside a laboratory environment, generally near to, or at the side of, the patient;

Classification

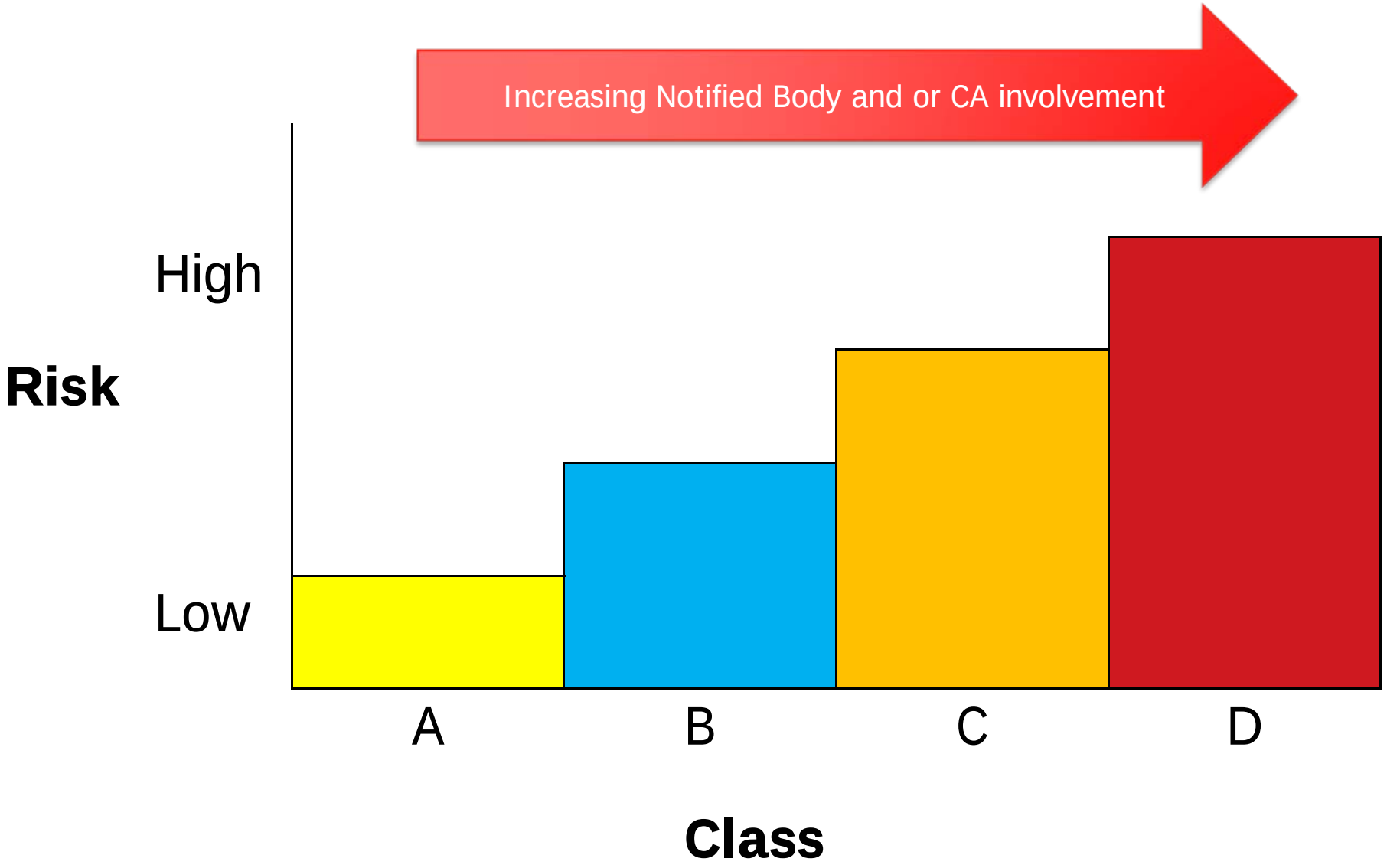
Class B

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

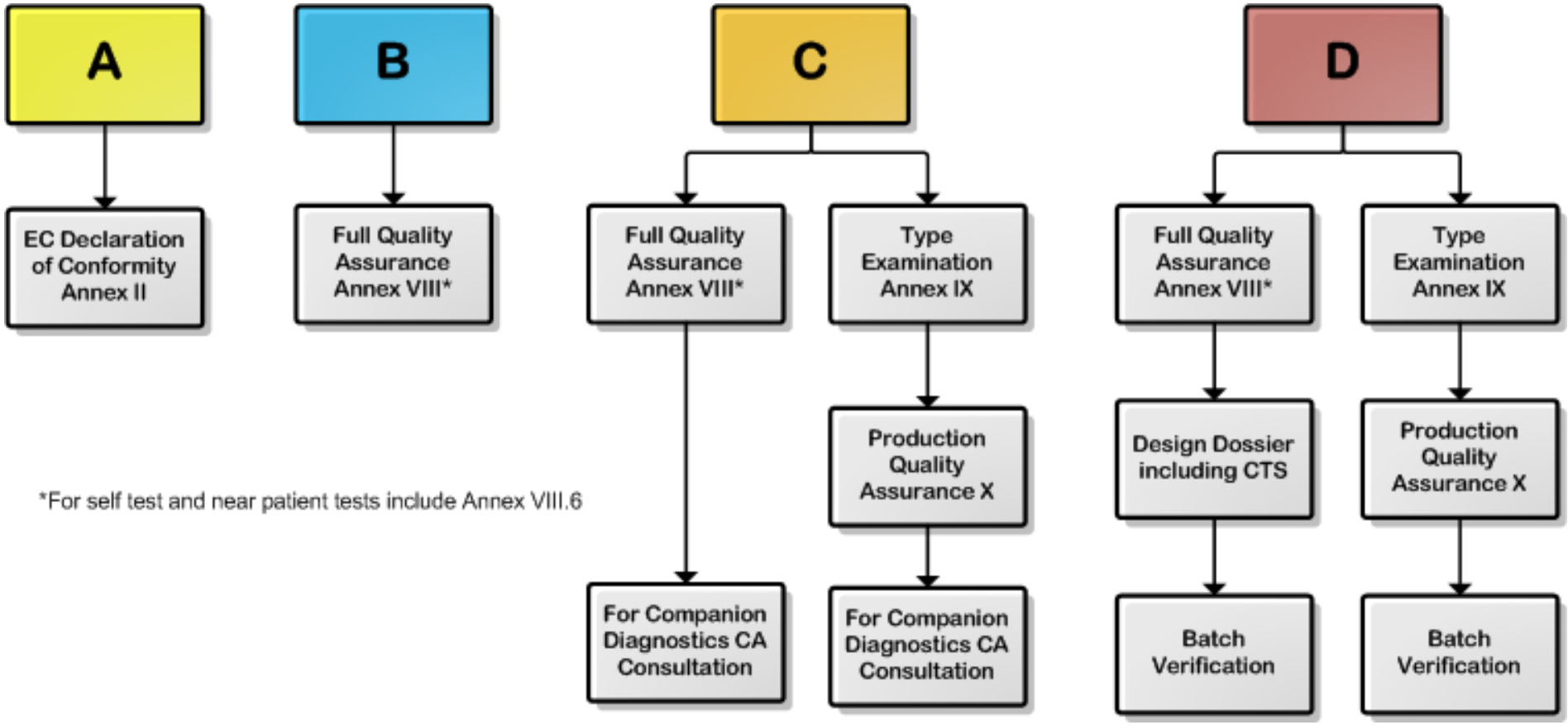
Class A

- Reagents, other articles with specific characteristics.
- Instruments intended specifically for use in IVD procedures.
- Specimen receptacles.

Conformity Routes



Conformity Assessment Routes



*For self test and near patient tests include 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

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.

Additional Requirements for Class D Devices

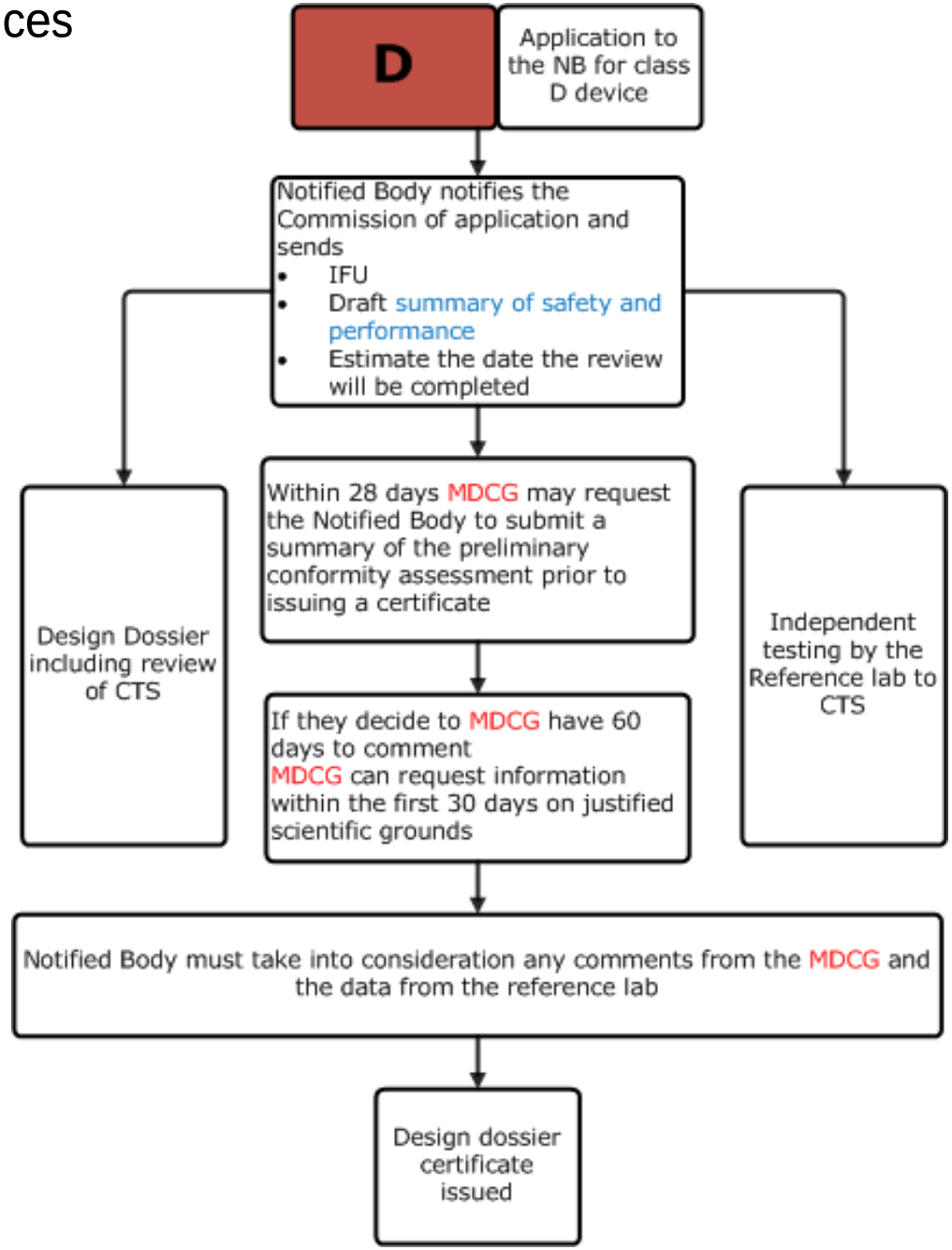
Medical Device Coordination Group (MDCG)

Contribute to
- the assessment of Notified Bodies
- the scrutiny of certain conformity assessments
- the development of guidance in particular
    - the designation and monitoring of NBs,
    - application of the general safety and performance requirements;

Assist Competent Authority in the coordination of clinical performance studies, vigilance and market surveillance;
Provide advice and assistance to the Commission;

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.



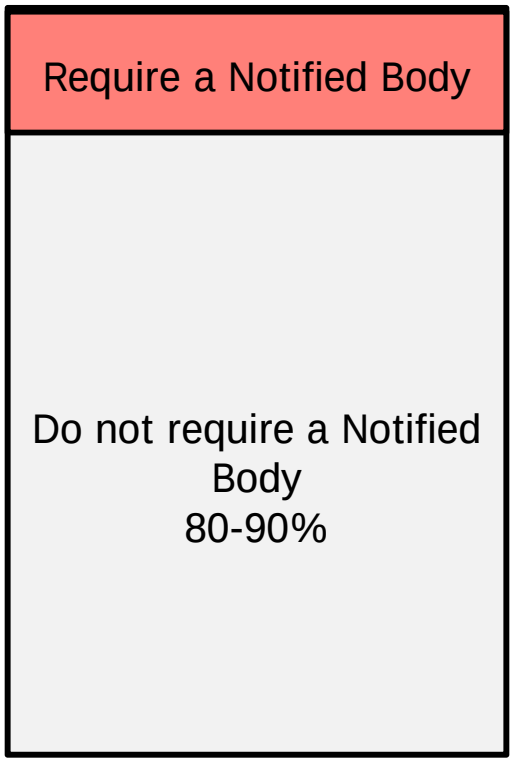
European Union reference laboratories

Within the scope of their designation, the EU reference laboratories shall, where appropriate, have the following tasks:

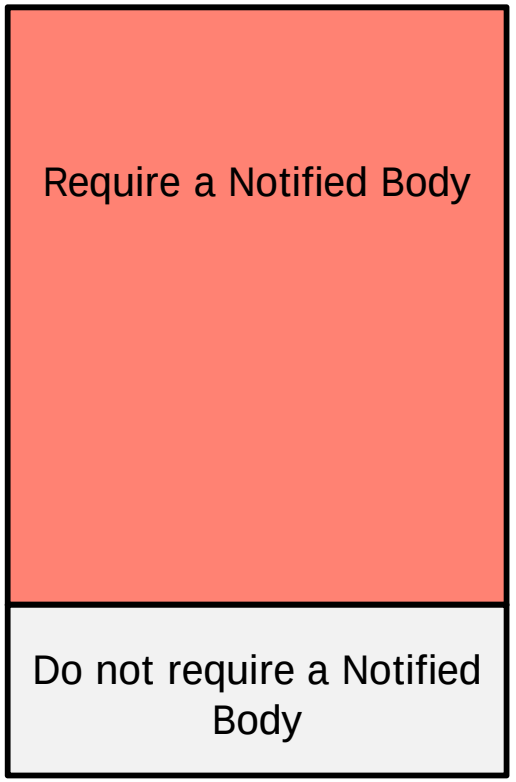
- to verify compliance of class D devices with the applicable CTS or with other solutions;
- to carry out testing of kit samples or batches of class D devices;
- to provide scientific and technical assistance to the Commission, the Member States and Notified Bodies in relation to the implementation of this Regulation;
- to provide scientific advice regarding the state of the art;
- to contribute to the development of appropriate testing and analysis methods for market surveillance;
- to collaborate with Notified Bodies in the development of best practices for the performance of conformity assessment procedures;
- to provide recommendations on suitable reference materials and reference measurement procedures of higher metrological order;
- to contribute to the development of standards at international level;
- to provide scientific opinions in response to consultations by Notified Bodies

Quantum Leap

IVD Directive



IVD Regulation



Clinical Expectations

Clinical Requirements

- Increased expectation for clinical requirements
- Demonstration of conformity with the general safety and performance requirements shall be based on clinical evidence unless duly justified
- Prepare a Clinical Evidence report which will include
  - scientific validity data,
  - the analytical performance data
  - the clinical performance data
- Clinical evidence is to be kept up to date during the life time of the device
- New definitions e.g. Likelihood ratio

  the likelihood a given result would be expected in an individual with the target clinical condition or physiological state compared to the likelihood that the same result would be expected in an individual without that clinical condition or physiological state

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Clinical Performance Studies

Clinical Performance Studies establishes the ability of a device to yield results that are correlated with a particular clinical condition or a physiological state in accordance with the target population and intended user it;

- shall be performed in circumstances similar to the normal conditions of use of the device.
- require a sponsor for overseas manufacturers as the primary contact
- need to meet good clinical practice requirements
- there are additional requirements for interventional clinical performance studies or other studies that involve invasive procedures or other risks to the subjects and this includes specimen collection pre and post CE marking

Clinical Requirements

Global Harmonisation Task Force documents were completed in 2012 even though the GHTF has been disbanded and will remain available In the IMDRF archive

- 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

Post Market Requirements

Increased requirements for Post Market Surveillance will include

- 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

Responsibilities in Europe

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;

Responsibilities

- Importers and distributors may become manufacturer if they:
  - make available on the market a device under his name, registered trade name or trade mark;
  - change the intended purpose of a device already placed on the market or put into service;
  - modify a device already placed on the market or put into service in such a way that compliance with the applicable requirements may be affected.

- Importers and distributers who translate instructions for us or repackage devices must
  - conduct these activities under a QMS to ensure they preserve the original condition of the device
  - a certificate from an appropriate Notified Body will be required for the QMS
  - procedures ensuring that the distributor or importer is informed of any corrective action taken by the manufacturer in relation the safety of the device or conformity with this Regulation.
  - inform the manufacturer and the competent authority
  - they can request a sample of the relabelled or repackaged device, including any translation

Registration

- The manufacturer, authorised representative and importers are required to register in the European database
- Importers must register within a week of placing on the market and also update any changes within a week
- Data must be verified bi-annually if it is not the products could be restricted/ excluded from Europe
- The database will be accessible to the public
- All economic operators will have to register within 6 months of the regulation becoming applicable i.e. the start of the transition period

Authorised Representative

- The manufacturer shall designate a single authorised representative.
- The authorised representative position needs to be accepted in writing by the authorised representative
- A mandate is required between the manufacturer and the authorised representative defining roles as described in the regulation
- The mandate will include the modalities for changing authorised representative
- Where manufacturers have their devices designed and manufactured by another legal entity, the information on the identity of that person shall be part of the registration, note this will be visible on the registration database to the public

Traceability in the Supply Chain

- For devices, other than devices for 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 place 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 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

Qualified Person

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

  or
  - 5 years of professional experience in regulatory affairs or in QMS relating to IVDs

- The qualified person 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
- The qualified person should suffer no disadvantage by performing their roll
- Authorised representatives will also be required to have a qualified person within their organisation

Distance Sales

- A device offered over the web to patients in Europe described in the regulation as “by means of information society services in Europe” must comply with the regulations at the time it is placed on the market
- Devices that are not placed on the market in Europe but are used in the context of a commercial activity to provide a diagnostic or therapeutic service by means of information society services to European citizens must also meet the regulation

Unannounced inspections
STARTING 2014

- At least once every third year but increase the frequency of unannounced audits if the devices bear a high risk, frequently non-compliant or if reasons to suspect non-conformities of the devices or of their manufacturer.
- The timing of the unannounced audits should be unpredictable. As a general principle an unannounced audit should not take less than one day and should be executed by at least two auditors.
- Notified bodies may visit premises of critical subcontractors or crucial suppliers if this is likely to provide more pertinent information. In particular if main part of design development, manufacturing, testing or another crucial process is located there.
- Notified bodies should check a recently produced adequate sample, preferably from the on-going manufacturing process, for its conformity with the technical documentation and with legal requirements.
- The check should encompass a file review and a test.
- Test may also be performed by manufacturer under observation of the notified body ("witness testing").
- The check of the conformity of device should include verification of traceability of all critical components and materials.
- There are specified requirements for sampling technical documentation and also auditing manufacturing on-going at time of unannounced audit

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Final Summary

- The new regulation has increased requirements/ expectations
- Important to read and understand the impact to your organisation
- This may seem in the distant future, however, unannounced visits start in 2013.
- The changes will impact
  - products in development now
  - contracts being prepared with economic operators
  - resource to generate the technical documentation
  - Identify and train qualified person
- Talk to your notified body about their plans for designation and resource
- Discuss at implementation at management reviews
- Track changes
- Be prepared!!

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