...making excellence a habit.™

European IVD Regulations and Risk Based Classification

An Overview for Global Quality Professionals

Sue Spencer
Head IVD
Oct 2013

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

Why?

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

What?

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)

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

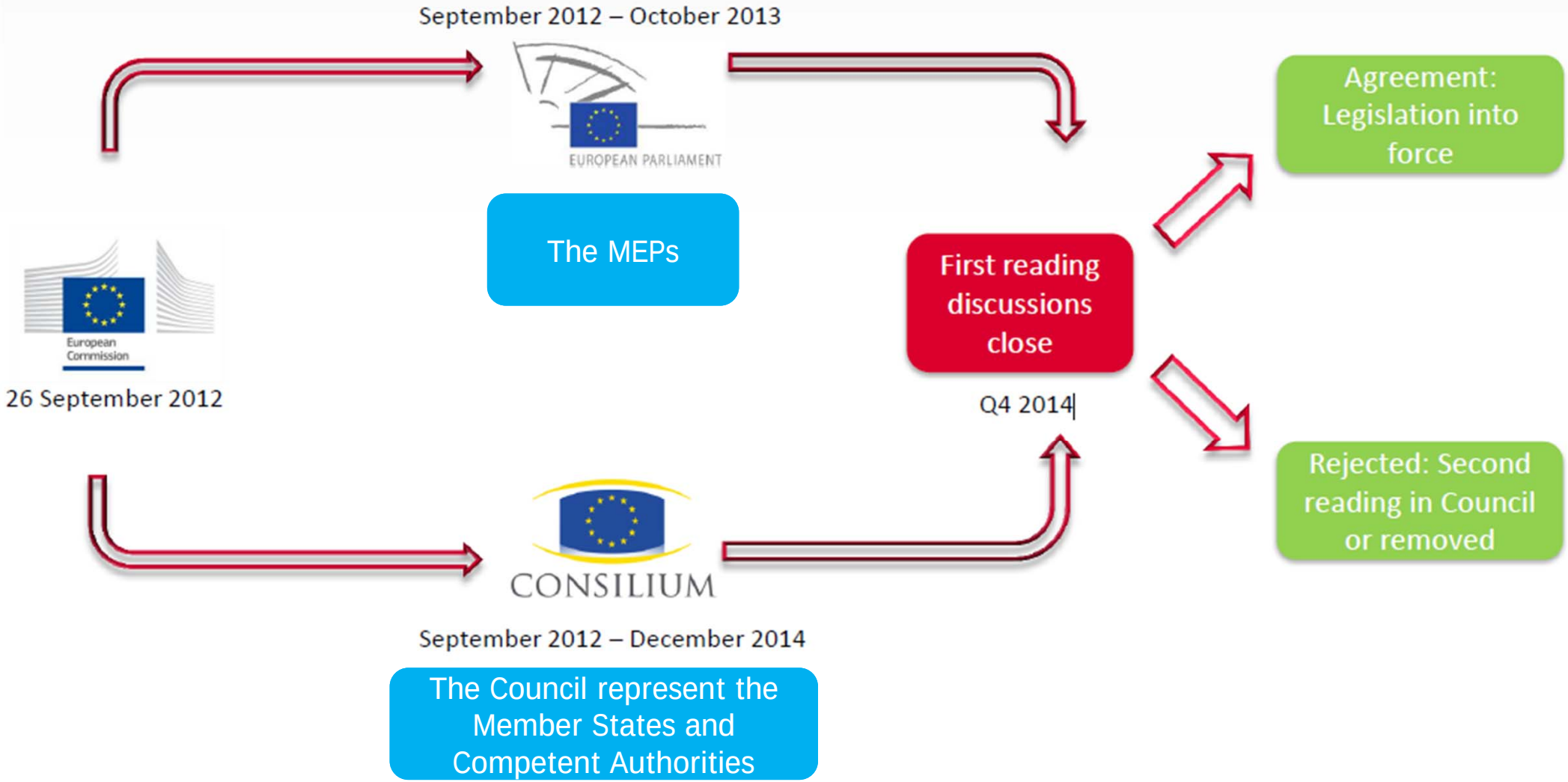
Annex XIII Interventional Clinical Performance Studies

Annex XIV Correlation table

More detailed consistent with the proposed Medical Device Regulation

When?

Legislative process - overview



Legislative process – Scenario One

26 September 2012
European Commission submits proposal to EP and Council

Sep 2012 – May 2013
EP review

18 June 2013
IMCO vote*

21 June 2013
EMPL vote*

18 Sep 2013
ENVI vote*

22 Oct 2013
Plenary vote on final EP

Q4 2013 – Q2 2013
Intensified discussions and analysis in the Council

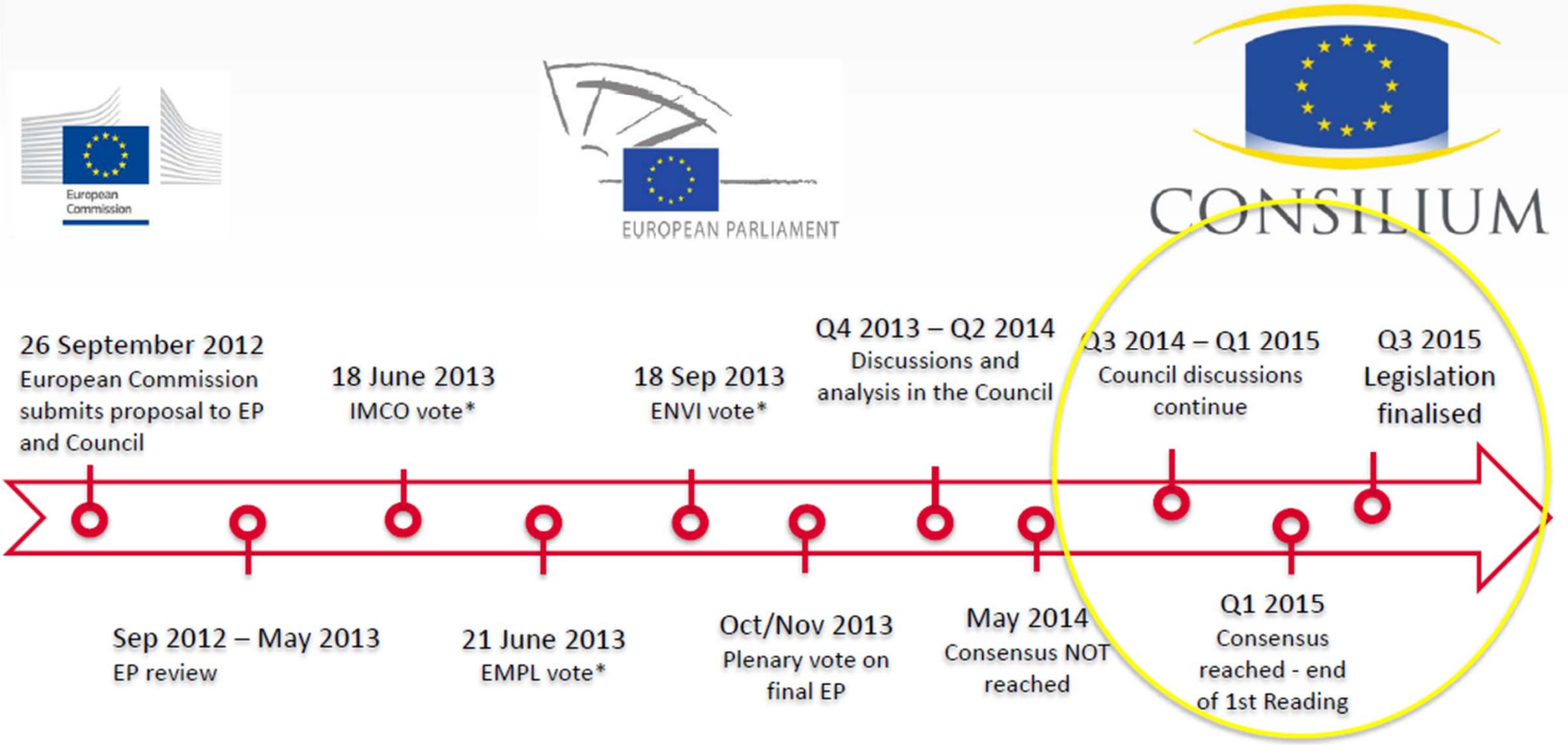
May 2014
Consensus reached – end of First Reading

Q4 2014
Legislation finalised

* IMCO and EMPL vote only on their own amendments, the ENVI Committee votes on all amendments.

bsi.

Legislative process – Scenario Two



Timeline

NOW

ENVI Vote → Plenary Vote → Council → Second Reading

Adoption → Implementing Acts → Transition → Enforced

IVDR 2014-2015

3 Years

IVDR must be applied 2018-2020

bsi.

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 (TBD)

The Basics of the IVDR

Classification and Conformity

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:

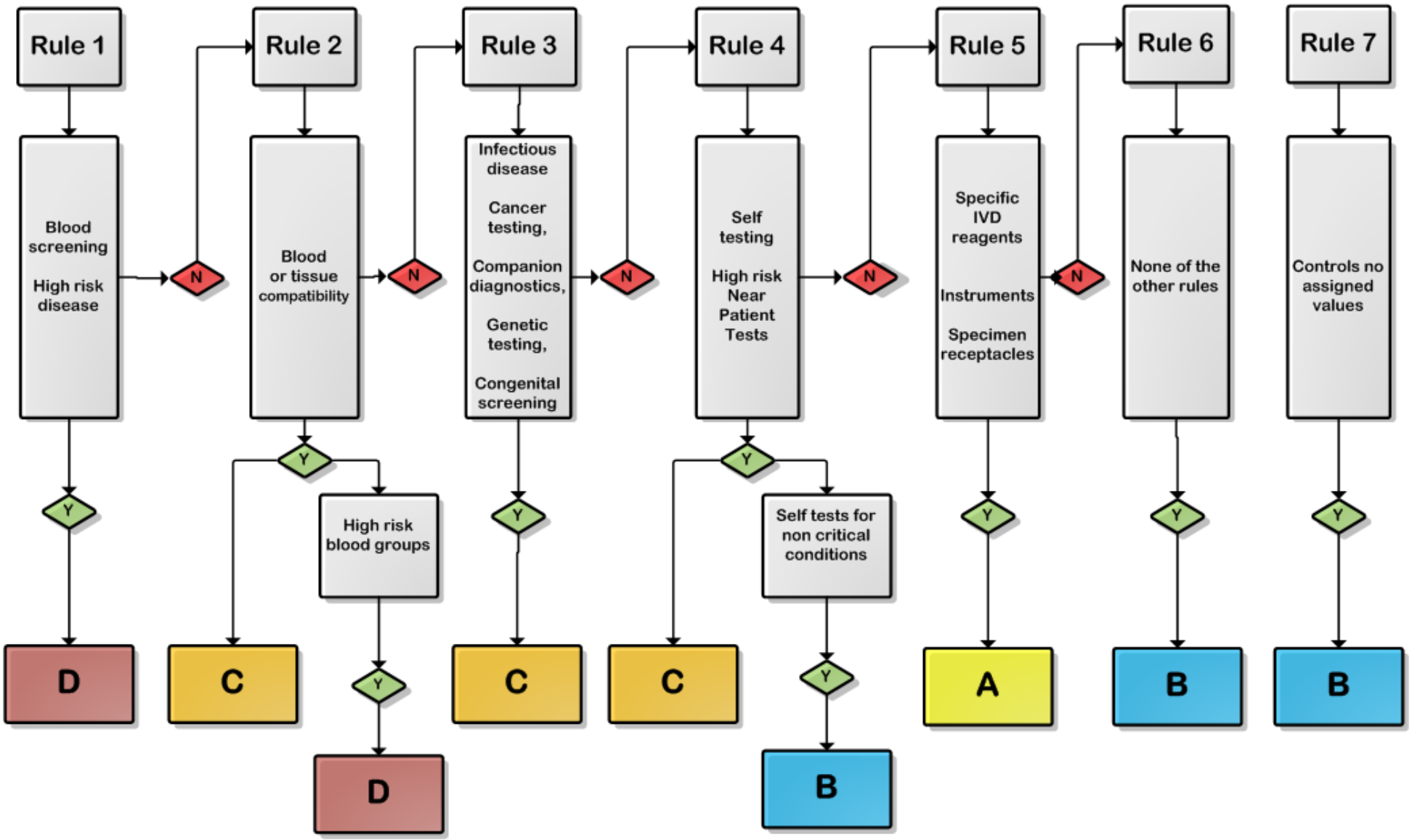
- concerning a physiological or pathological state;
- concerning a *physical or mental impairments*;
- concerning the predisposition to a medical condition or a disease;
- to determine the safety and compatibility with potential recipients;
- to predict treatment response or reactions;
- to define or monitor therapeutic measures.

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

Commission Justification

So called lifestyle-tests should fall under the regulation as they could have enormous consequences for the health of the patient/consumer. An extended scope therefore is important for protection of patients and consumer in Europe.

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

*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
  - 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.

*Genetic testing
means an IVD the purpose of which is to identify a genetic characteristic of a person which is inherited or acquired during prenatal development;

*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

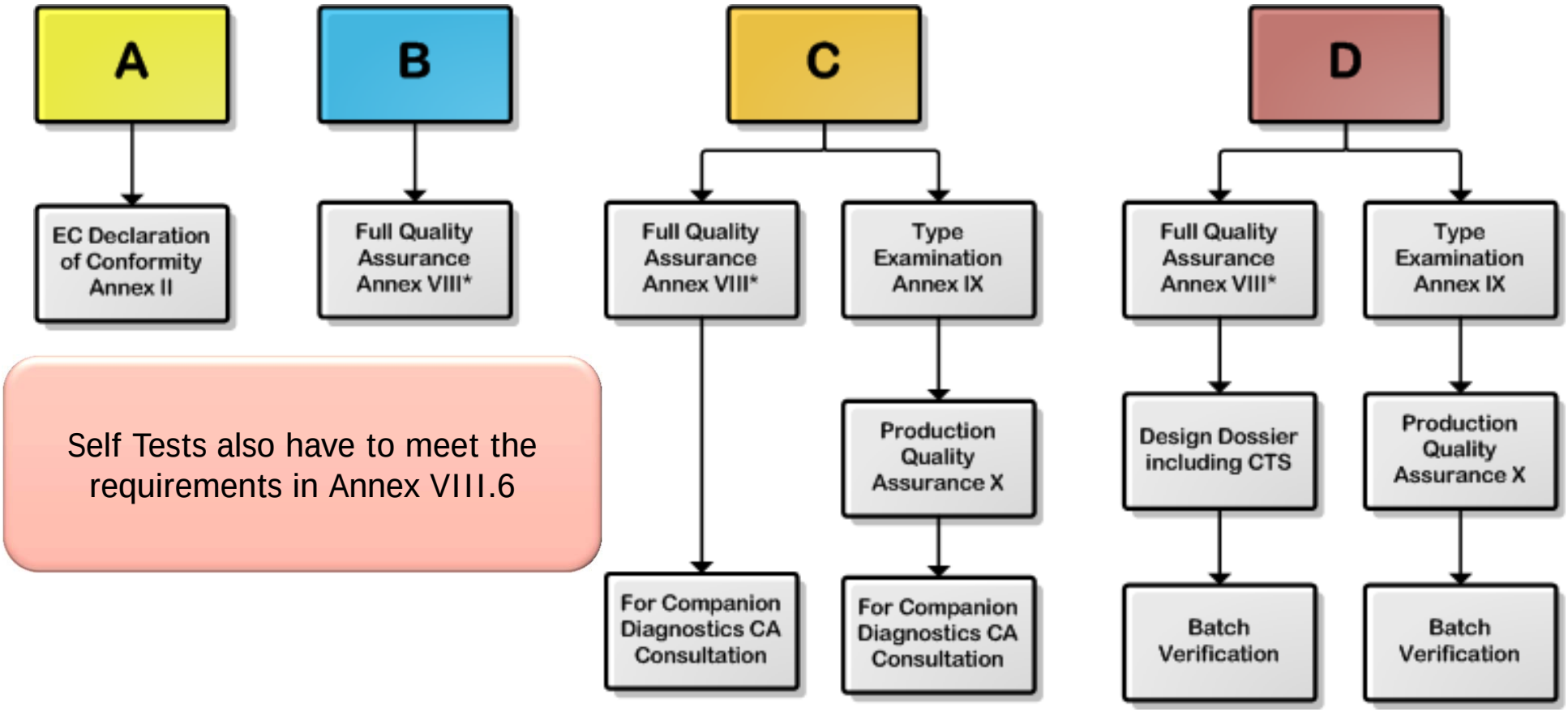
- Any IVD not listed under Classes D, C or A.
- Controls without an assigned value.

Class A

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

There will be clarification to the classification but no substantial change

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.

Designation of Notified Bodies and Special NBs

No Notified Body Class A

Notified Body Class B & Class C

Special Notified Body Class D

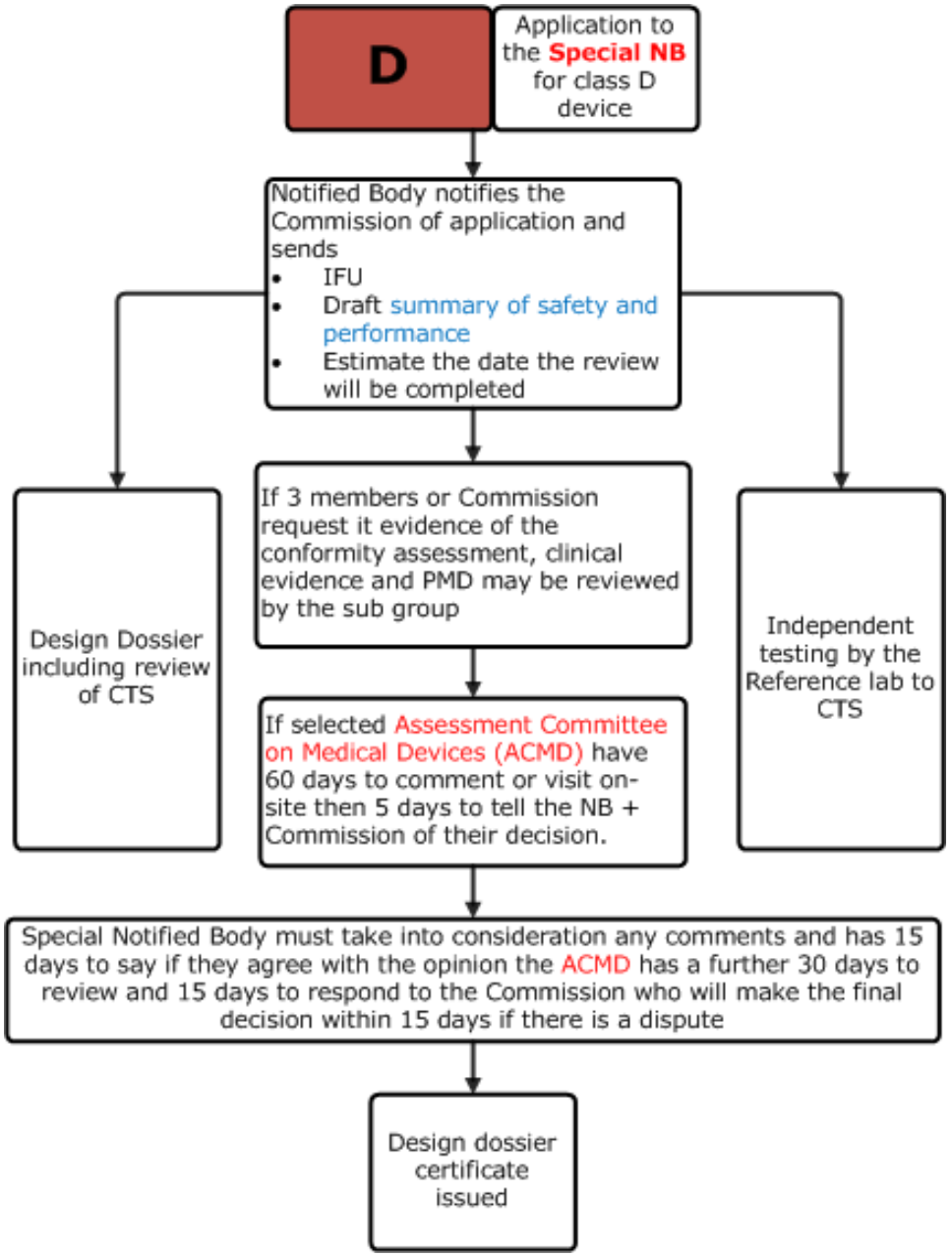
Additional Requirements for Class D Devices

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.

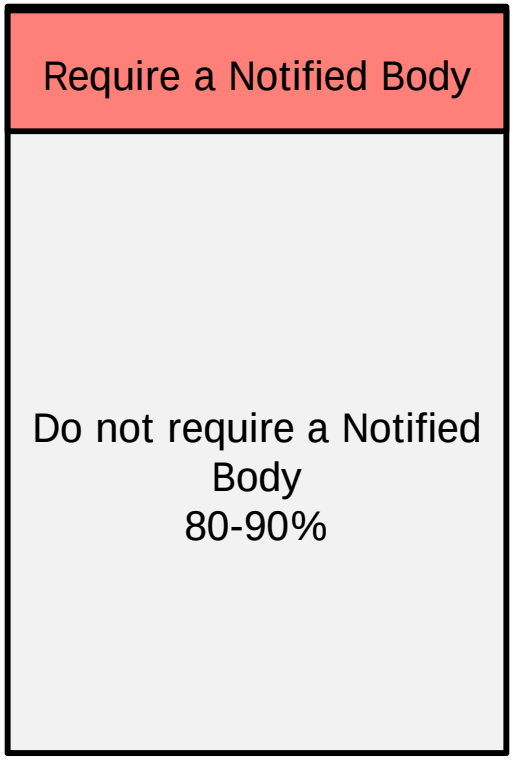
SUBJECT TO DISCUSSION

- Highly likely to be some form of scrutiny for selected high risk devices
- Changed from the Medical Device Coordination Group (MDCG) to the Assessment Committee of Medical Devices (ACMD)
- There will be delays compared to the current process
- There may be additional fees

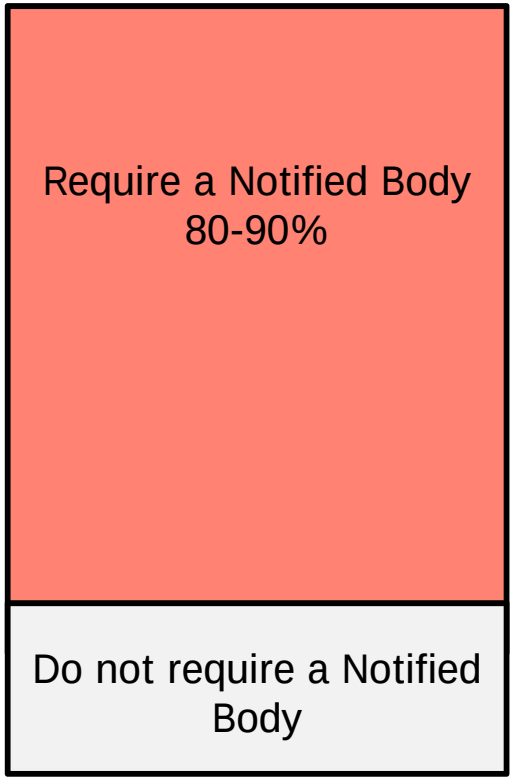


Quantum Leap

IVD Directive



IVD Regulation



Latest Changes and Hot topics

Latest Changes introduced by the amendments

- Clinical expectations including Ethics & Informed consent
- Transparency
  Increased public visibility to Clinical/ NB/ subcontractor data
- Control Notified bodies
  Increased supervision, requirement for in-house expertise and assessor training
- In house testing
  Class D can no longer be exempt if there is an existing CE marked device
  Hospital labs developing LDT have to be accredited to ISO15189
  Tests and testing services provided to EU citizens need to meet the IVDR
- Control of the supply chain
  New requirements for suppliers and subcontractors and also distributors, importers and authorised representatives
- Person responsible for regulatory compliance
  Required by the manufacturer and authorised rep with degree or 3 years experience in IVDs
- Unannounced audits

bsi.

Clinical Expectations

Clinical Requirements

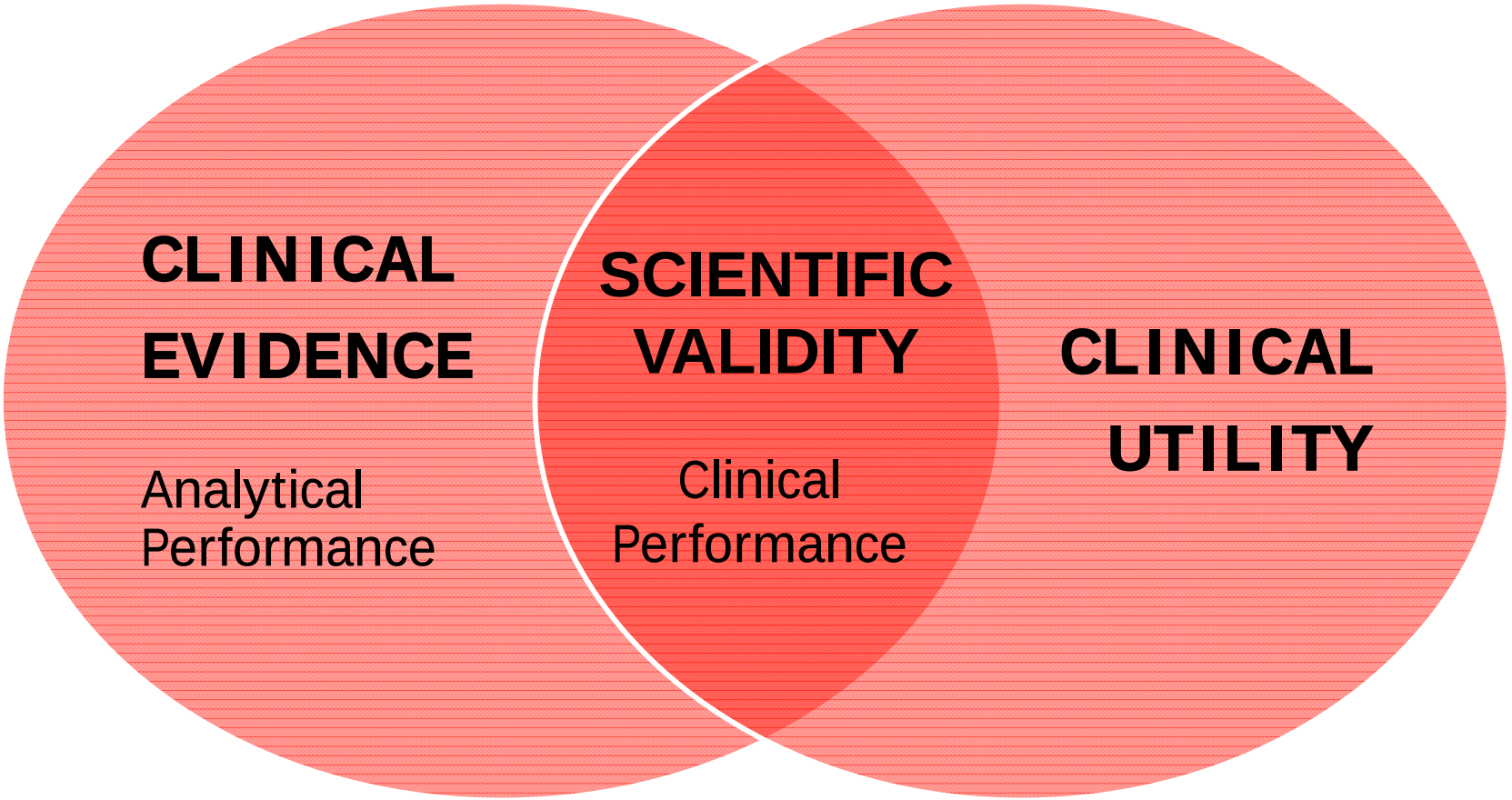
- Increased expectation for clinical requirements
- Clinical evidence is to be kept up to date during the life time of the device

The GHTF documents now in the IMDRF archive best guidance

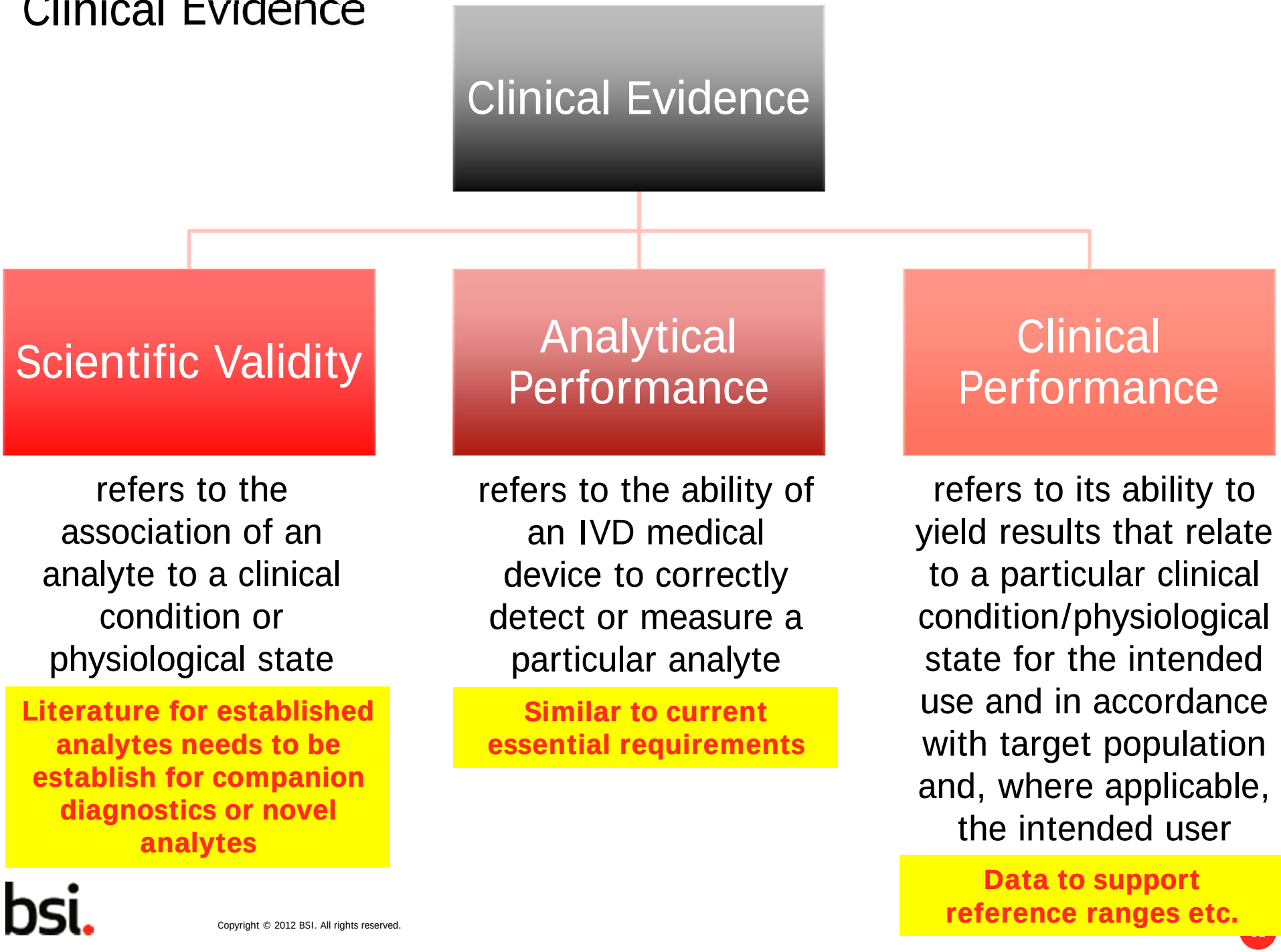
- Clinical Performance Studies for In Vitro Diagnostic Medical Devices
- Clinical Evidence for IVD Medical Devices – Key Definitions and Concepts
- Clinical Evidence for IVD Medical Devices – Scientific Validity Determination and Performance Evaluation

bsi.

Clinical Evidence



Clinical Evidence



Clinical Performance

- Objective evidence is required of the clinical performance, information may include
- data from clinical performance studies,
- scientific literature
- experience gained by routine diagnostic testing
- or a combination of the above

- Clinical performance studies shall be performed where the information and/or data from the scientific literature or experience gained by routine diagnostic testing is insufficient to demonstrate conformity with the applicable clinical performance characteristics of the device.

- Need to justify why studies are not required

bsi.

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
- Has never been a regulatory requirement in Europe
- Clinical Utility is still under discussion but likely to be required for Companion Diagnostics, the proposed amendment states

For a companion diagnostic, the manufacturer should supply clinical evidence relating to the impact of a positive or negative test on

(1) patient care; and

(2) health outcomes, when used as directed with the stated therapeutic intervention.

For companion diagnostics, the relevant target population and directions for use with the associated therapeutic(s) should be made clear in the technical documentation.

Interventional studies

- New requirements for interventional clinical performance studies and other performance studies involving risk's for the subjects of the studies
- In the IVDD there was an assumption that IVD studies did not create a risk to the patient.
- Due to the advent of Companion Diagnostics and genetic testing this is no longer the case
- IVDR includes requirements for ethics committee approvals
- New requirements detailing the requirements to protect the rights of minors and the incapacitated during such studies which could impact prenatal and neo natal testing
- New requirements addressing the need to supply genetic counselling especially to minors for genetic diseases which do not develop till adulthood. These requirements are directed to the members state not industry or the notified bodies

Conclusion Clinical Evidence

- Will be required in the EU
- Ideally, it already should be considered especially for new parameters
- Plans for the determination of scientific validity for new analytes may take significant time and best addressed as part of product design and development.

- Clinical evidence needs to be kept up to data and there are additional requirements for post market surveillance

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

bsi.

Responsibilities of the manufacturer, importer and distributers 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;

Increased Control of the Supply Chain

Manufacturer

Crucial Suppliers

OEM's

Sub contractors

Distributers

Importers

Authorised Representatives

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

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

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.*

Emerging Pathogens

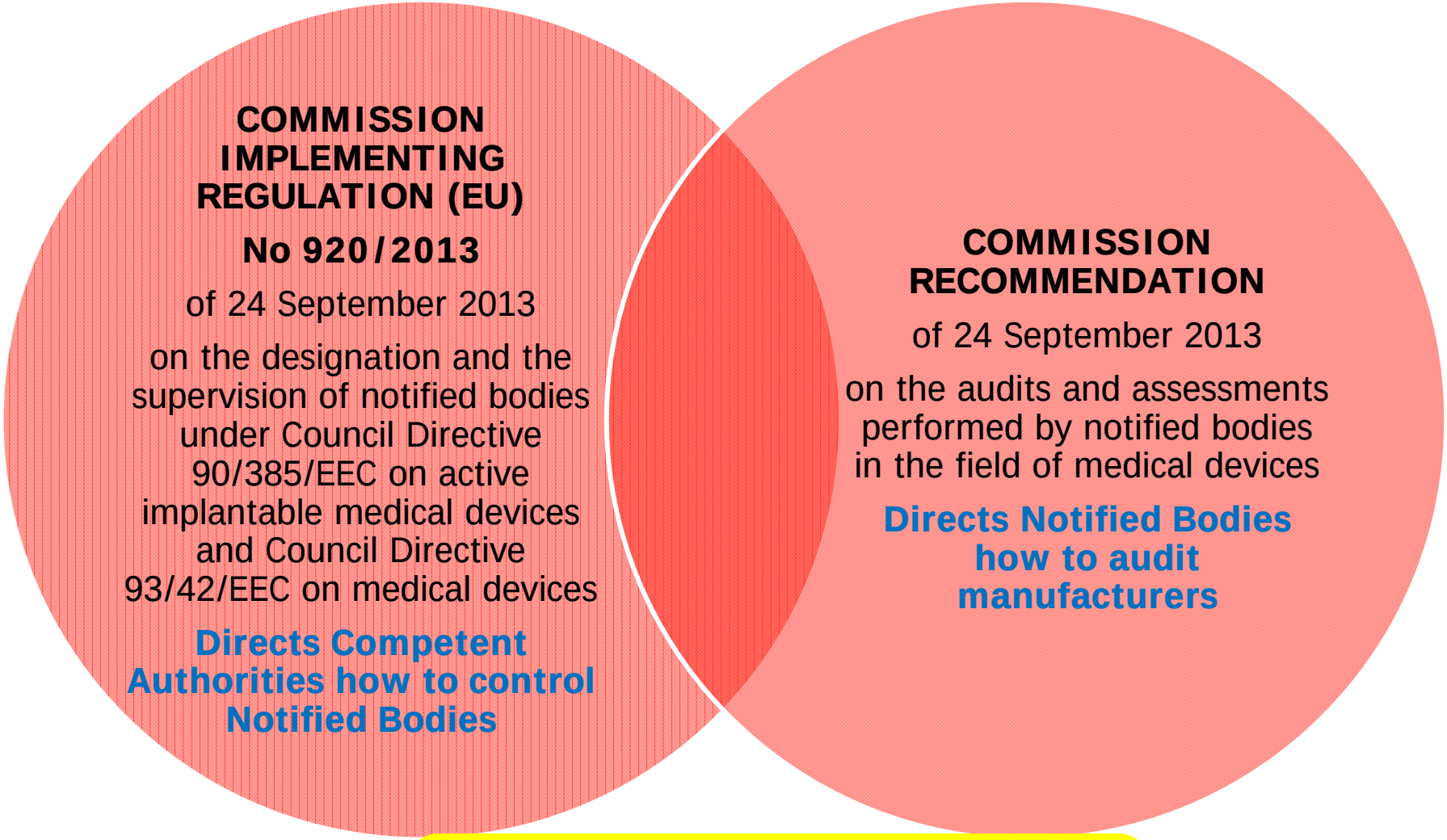
- *In the case of urgent or unmet medical needs for patients, such as emerging pathogens and rare diseases, single health institutions should have the possibility of manufacturing, modifying and using devices in-house and thereby addressing, within a non-commercial and flexible framework, specific needs 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.*

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.

Unannounced visits

Recently Published



Effective from Jan 2014

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”

Unannounced Audits
STARTING 2014

- At least once every third year and 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.

bsi.

Unannounced Audits
STARTING 2014

- 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
- Audits will be at least 2 assessors for 1 day
- 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

According to the latest amendments he IVDR may require ANNUAL unannounced audits

bsi.

What can you do now to prepare 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

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

Any Questions

Name: **Sue Spencer**

Title: Head IVD

Address: BSI

Kitemark Court,

Davy Avenue,

Milton Keynes, MK5 8PP, UK

Telephone: +44 (0)1908 814861

Mobile: +44 (0)77857 16906

Email: sue.spencer@bsigroup.com

Website: http://medicaldevices.bsigroup.com/ivd

...making excellence a habit.™