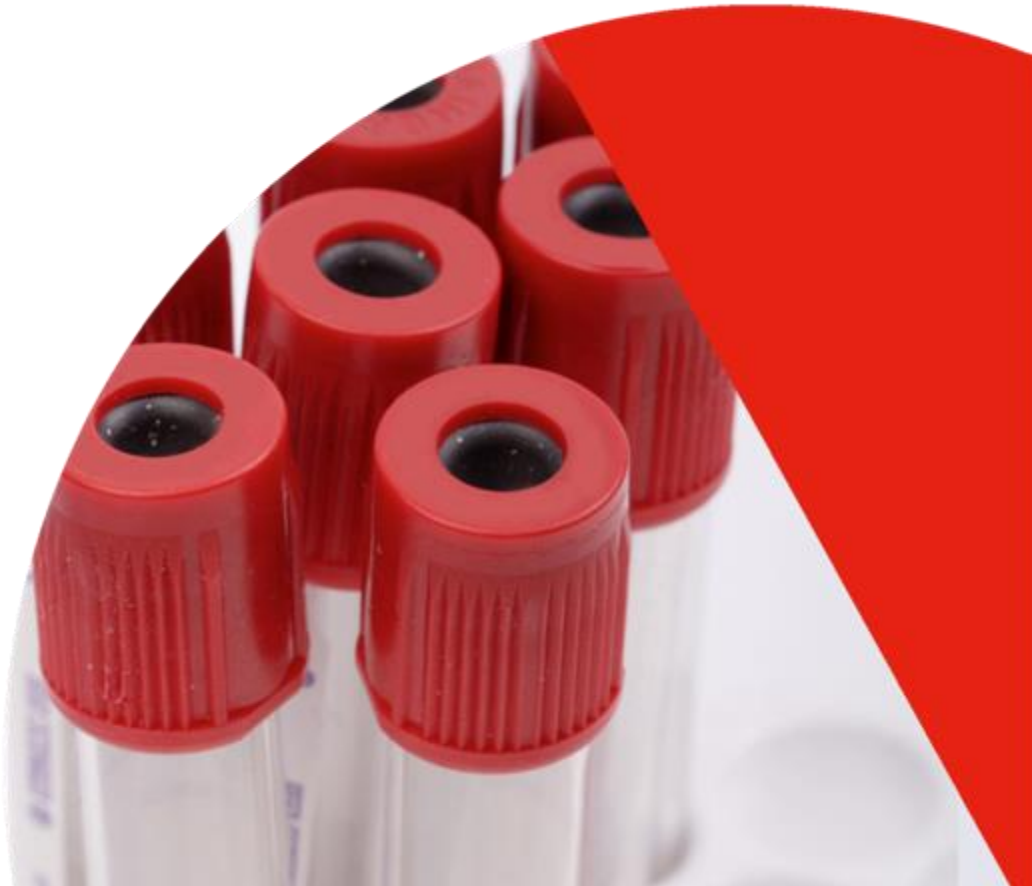
# IVD Regulation Update

AMDM Focus Meeting 2016

Stefan Burde



# IVDR Overview - Update

# Overview

## Key impacts for IVDs under the IVDR

1. Time line for IVDR
2. Scope
3. Classification
4. Conformity Assessment
5. Clinical Evidence
6. Scrutiny
7. Post-market
8. Companion Diagnostics
9. In-house Manufacture
10. Other Aspects of Significance

- What now…

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# 1. Time line

# 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 i.e. same text throughout EU
- Direct entry into force
- No Transposition period as it doesn't need transposing into Member State law
- There will be a transition period of 5 years
- The regulation identifies areas which can be updated in the future using additional implementing acts according to Article 84(3)

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# IVDR update

## Medical devices: deal reached on new EU rules

25/05/2016 | 20:15 | Press release | 283/16 | Health

On 25 May 2016, the EU agreed new rules on medical devices and in vitro diagnostic medical devices.

The Netherlands presidency of the Council and representatives of the European Parliament reached a political agreement. It is still subject to the approval by the Council's Permanent Representatives Committee and of the Parliament's ENVI committee.

- Political agreement has been reached between Council and Parliament
- Consolidated *draft* text issued dated 15-Jun; clean version 27-Jun-2016
- Translation of text and legal linguist review
- Formal adoption of text by Council and Parliament – expected Nov 2016
  - Vote to open interinstitutional negotiations on Draft Agenda for 5 Nov ENVI committee session
- Publication in the *Official Journal of the EU*

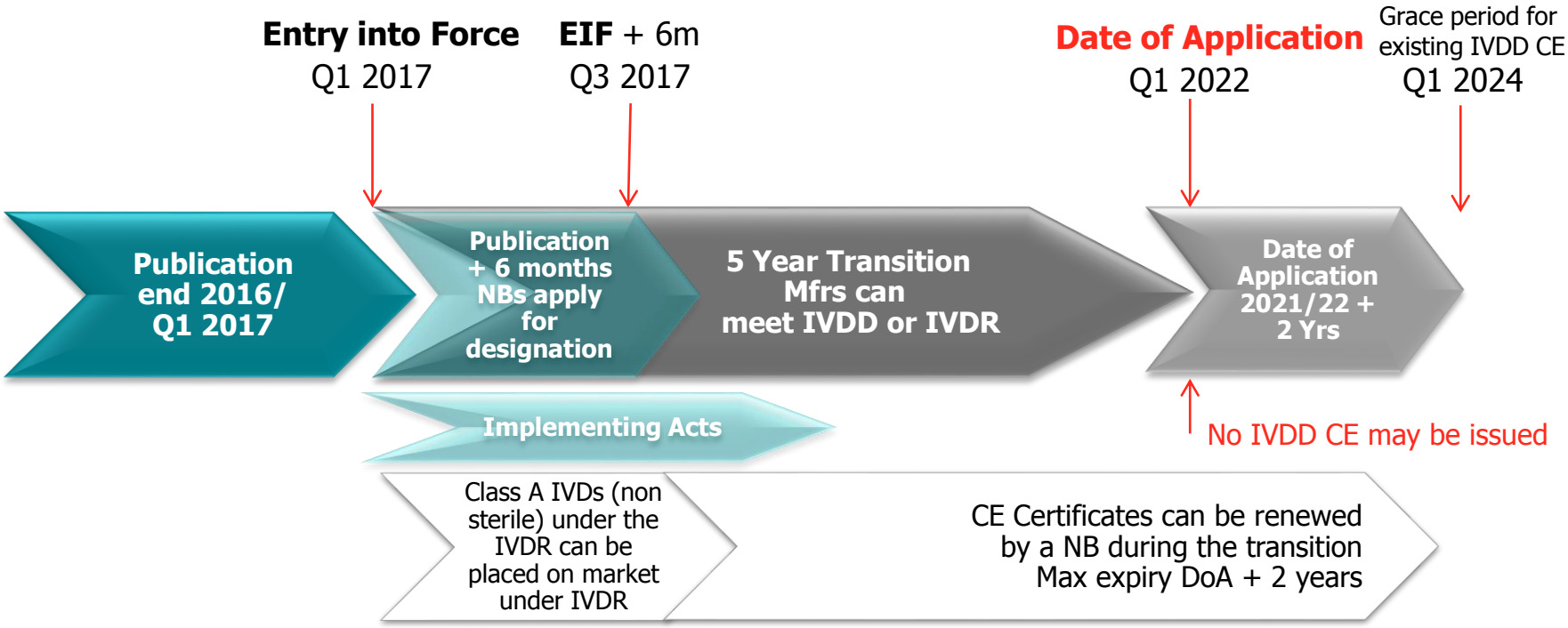
# IVDR update

**Medical devices: deal reached on new EU rules**

## Alignment of the MDR and IVDR

- '…There are specific features of *in vitro* diagnostic medical devices, in particular in terms of risk classification, conformity assessment procedures and clinical evidence, and of the *in vitro* diagnostic medical device sector which require the adoption of a specific legislation, distinct from the legislation on other medical devices,
- whereas the horizontal aspects common to both sectors should be aligned.'

# Transitional arrangements for IVDR



# 2. Scope

# Scope – Definitions that apply

## Medical Device

- ‘medical device’ means 'medical device' as defined in Regulation (EU) No [Reference to the future Regulation on medical devices].

# Scope – Definitions that apply

## Medical Device

- 'medical device' means [illegible] as d[illegible] [Re[illegible] me[illegible]

## In Vitro Diagnostic MD

- …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…to be used *in vitro* for the examination of specimens, including blood and tissue donations… from the human body,
- solely or principally for…providing information..

# Scope – Definitions that apply


**Medical Device**

- 'medical device' means [illegible] as defined in [illegible] medical

**In Vitro Diagnostic MD**

- concerning a physiological or pathological **process or** state;
- concerning congenital **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.

# What is NOT an IVD…

- (a) products for **general laboratory use** or **research-use only products**, unless such products, in view of their characteristics, are specifically intended by their manufacturer to be used for in vitro diagnostic examination;
- (b) **invasive sampling devices** or those which are **directly applied to the human body for the purpose of obtaining a specimen**;
- (c) internationally certified reference materials;
- (d) materials used for external quality assessment schemes.

# Consideration of scope…

## Placing on the market

- *'placing on the market'* means the first **making available** of a device, other than a device for performance study, **on the Union market**;

- *'making available on the market'* means any **supply** of a device, other than a device for performance study, for **distribution**, **consumption or use** on the Union market in the course of a commercial activity, whether in return for payment or free of charge;

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- A device offered by means of *information society services* as defined in Article 1(2) of Directive 98/34/EC to a natural or legal person established in the Union shall comply with this Regulation

# Distance sales

- A device offered by means of “information society services” - this includes the internet

- A kit does not have to be sold in EU; the IVDR applies if it has been used to test EU citizens. The IVDR states if “a device that is not placed on the market but used in the context of a commercial activity, whether in return for payment or free of charge, for the provision of a diagnostic or therapeutic service offered by means of information society services or by other means of communication, directly or through intermediaries, to a natural or legal person established in the Union shall comply with this Regulation.”

- Competent authorities can ask the legally responsible manufacturer or body offering the device or providing a service to provide  a copy of their EU declaration of conformity of the device

- If a Member State has grounds for concern based on the of protection of public health, the provider will be required to cease its activity.

# 3. Classification

# New Classification of IVDs by risk

- Risk classes A, B, C & D (where D is the highest) – Annex VII
- Implementing acts and Guidance
- Borderline issues will be referred to the CA of the Manufacturer or Authorised Rep; if this is different to the CA of the NB, they will consult
- Role of Medical Device Coordination Group (MDCG)
- If there is more than one potential application for a test, and the intended use is of the lower classification, there must be a specific exclusion in the labelling
- Where more than one rule applies, the highest classification will be used.

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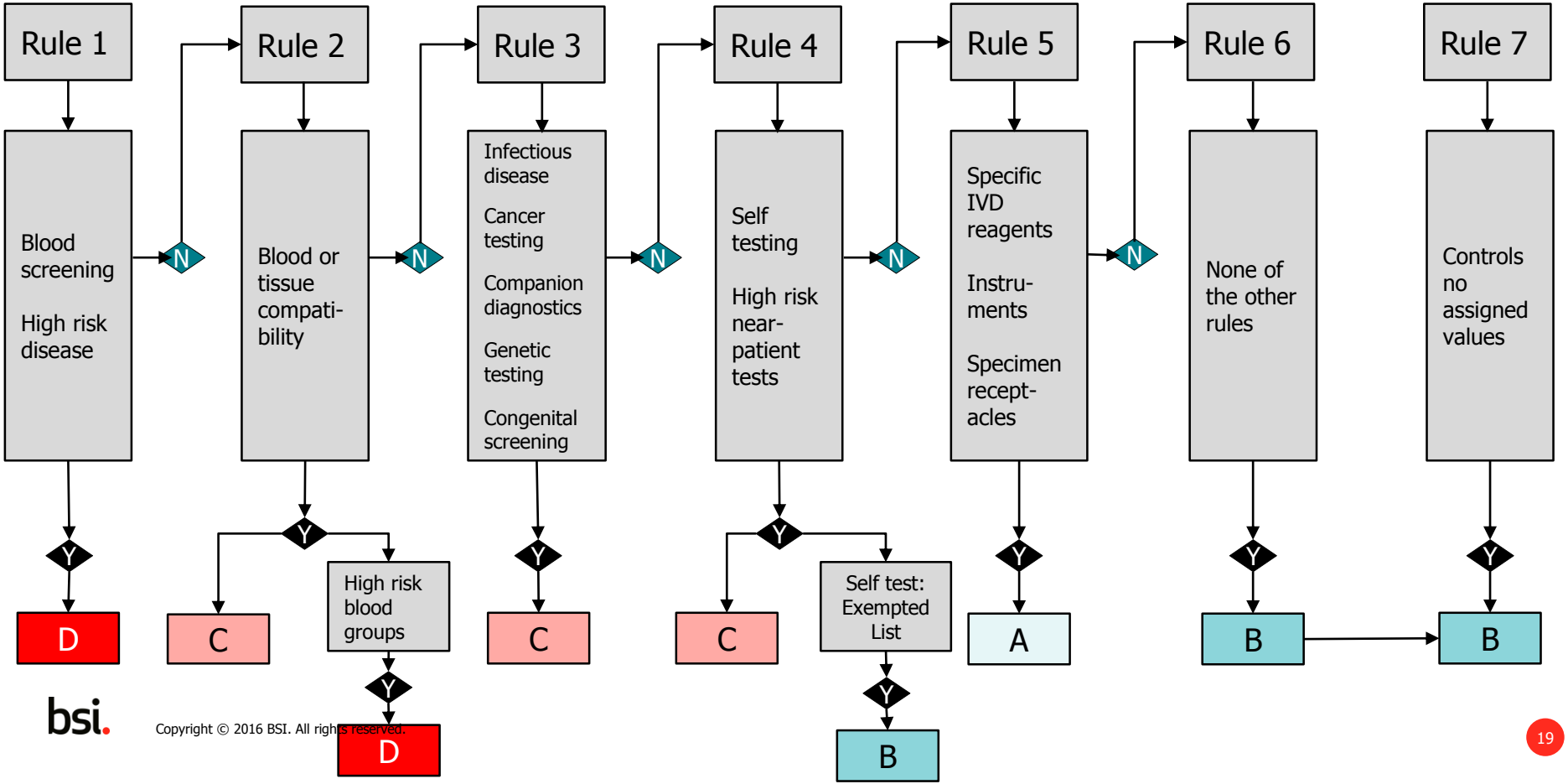
# Classification



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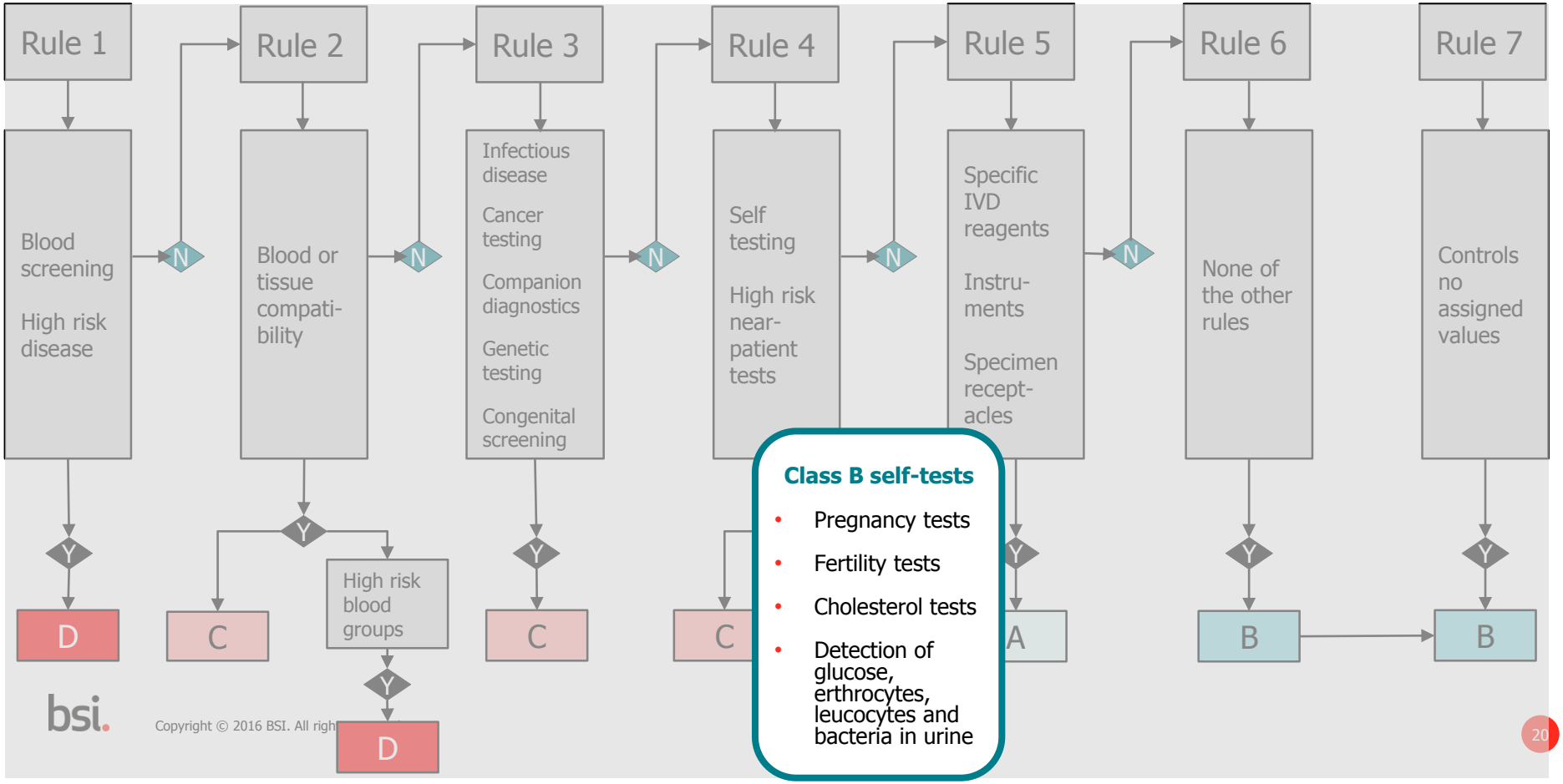

# New classes of IVD devices

## Class D

**High public health risk, high personal risk**

Examples

- HIV 1/2,
- Hepatitis C virus
- Hepatitis B virus
- HTLV I/II
- Blood grouping ABO, Rhesus (including RHW1), Kell, Kidd and Duffy systems
- CHAGAS
- Syphilis (used to screen blood donations)

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## Class C

**High personal risk, moderate to low public health risk**

- Syphilis (diagnosis only)
- Neonatal screening for metabolic disorders e.g. PKU
- Rubella
- Cancer markers
- Genetic tests
- Companion diagnostics
- Blood glucose meters/strips
- Blood gas analysers
- Self tests

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## Class B

**Moderate to low personal risk, low public health risk**

- Thyroid function
- Infertility assays
- Clinical chemistry

- Self-test devices listed as not Class C

- **'Near patient tests' are classified in their own right**

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## Class A

**Low personal risk, low public health risk**

- Accessories
- Wash buffers
- Specimen receptacles
- Instruments
- Culture media

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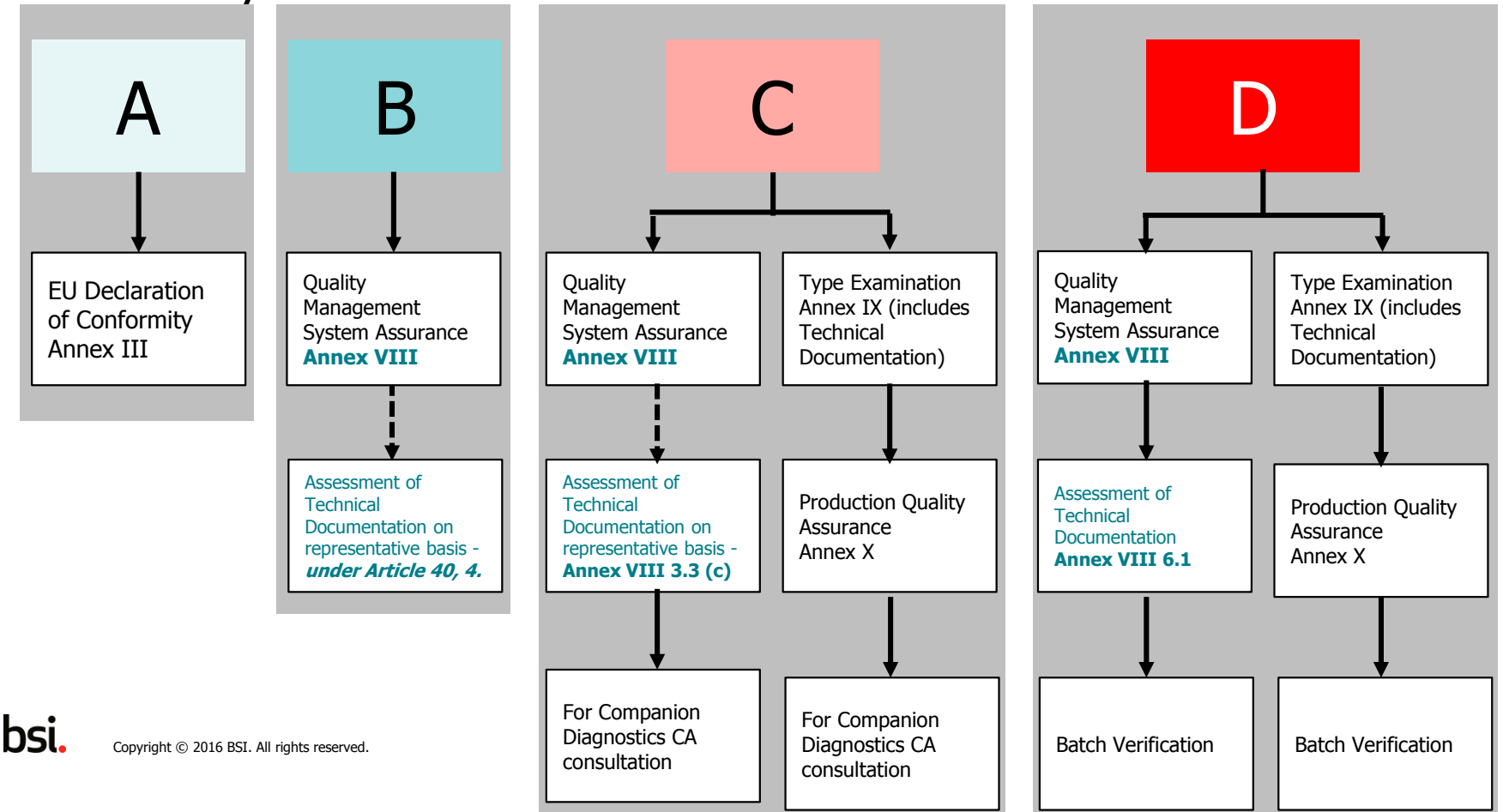
# 4. Conformity Assessment

# Conformity Assessment



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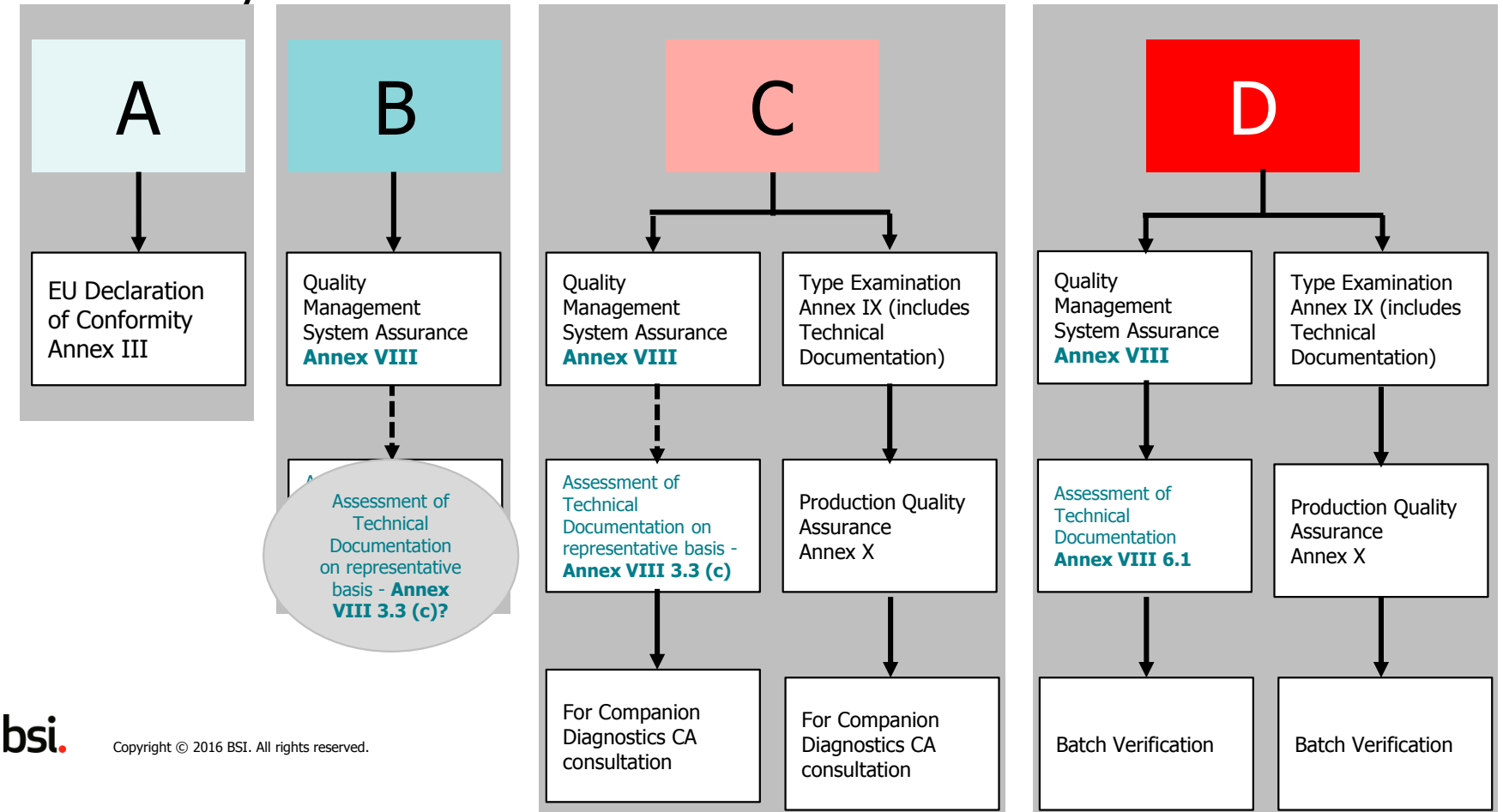
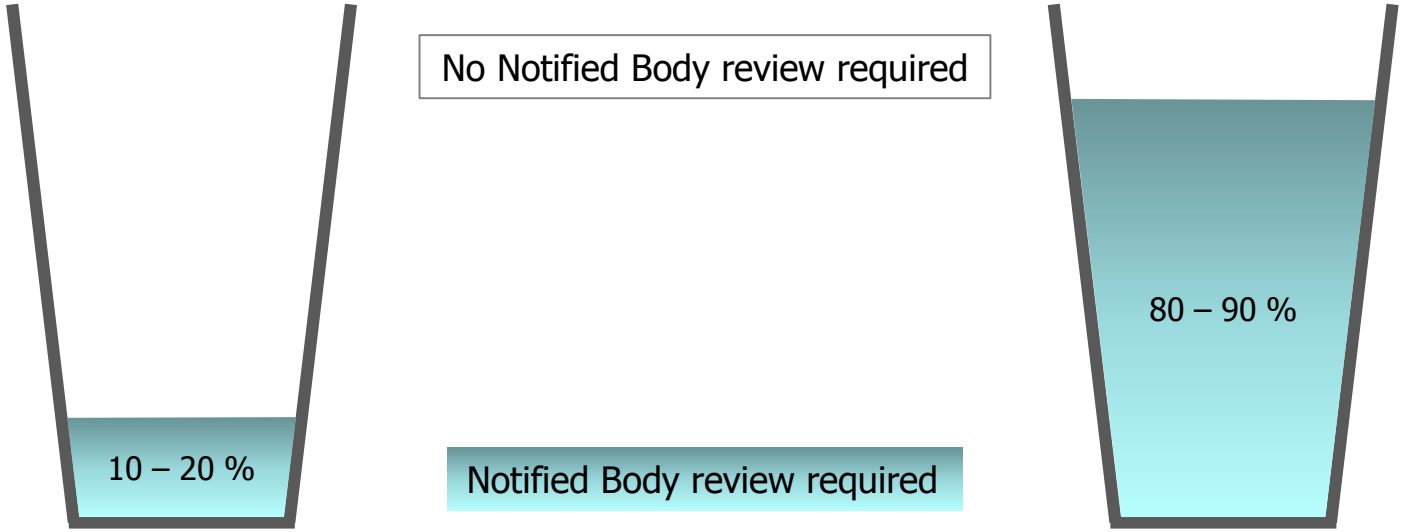


# A sea change for industry and regulators

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# 5. Clinical Evidence

# ‘Clinical benefit’ consideration

# Clinical Evidence

- New requirement for Clinical Evidence
- ***Clinical evidence*** *= clinical data and performance evaluation results, pertaining to a device of sufficient amount and quality to allow a qualified assessment of whether the device achieves the intended clinical benefit and safety, when used as intended by the manufacturer*

- Based on harmonised guidance
- **GHTF documents** (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

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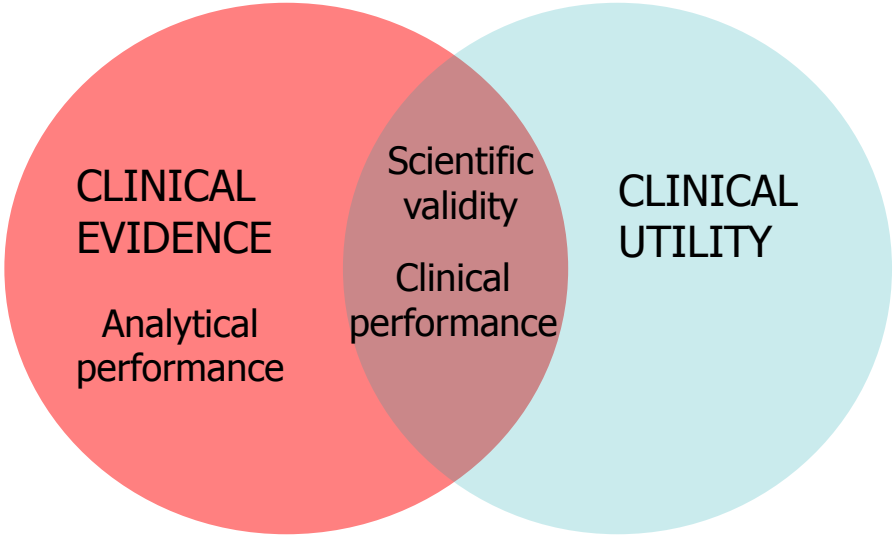


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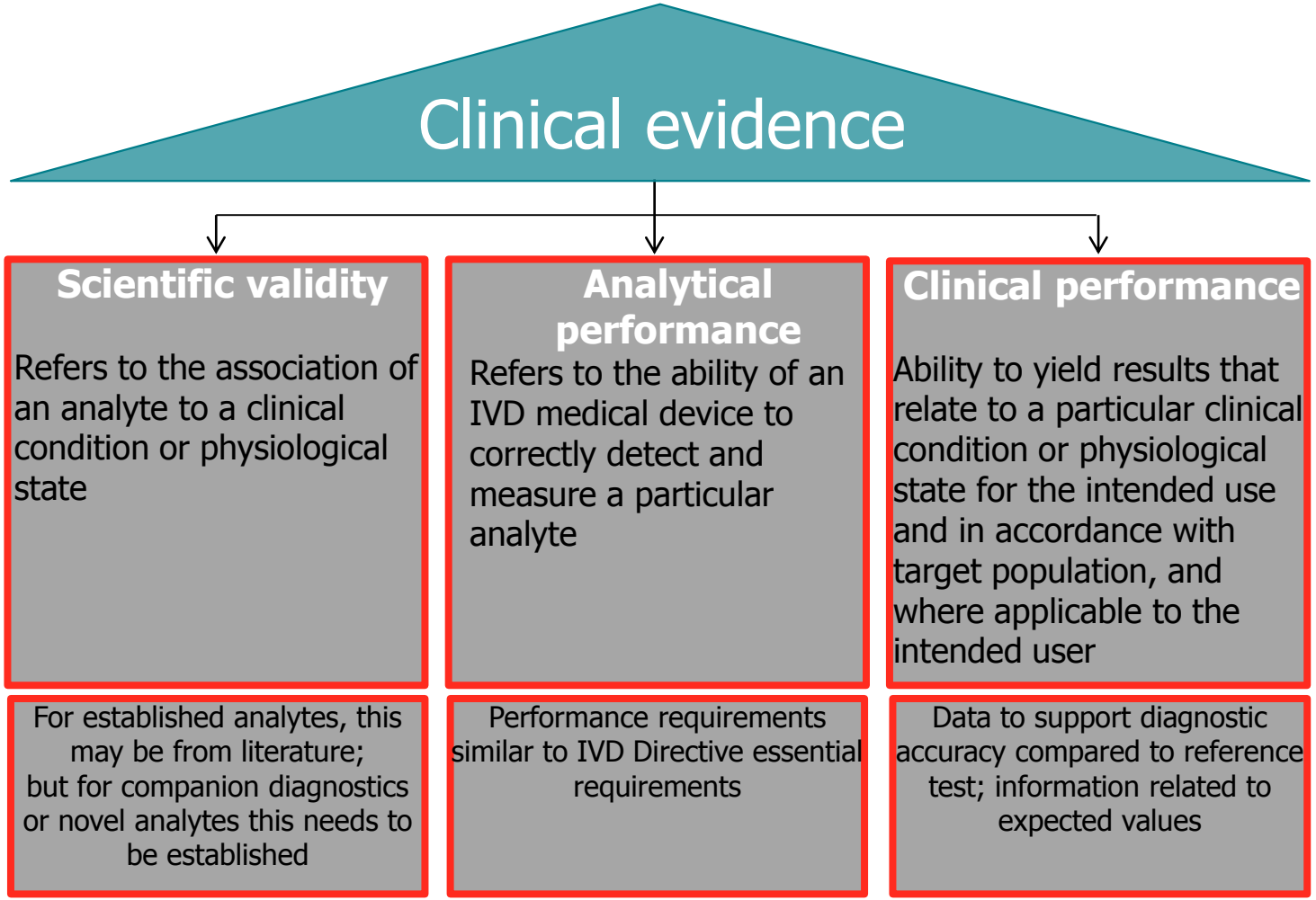
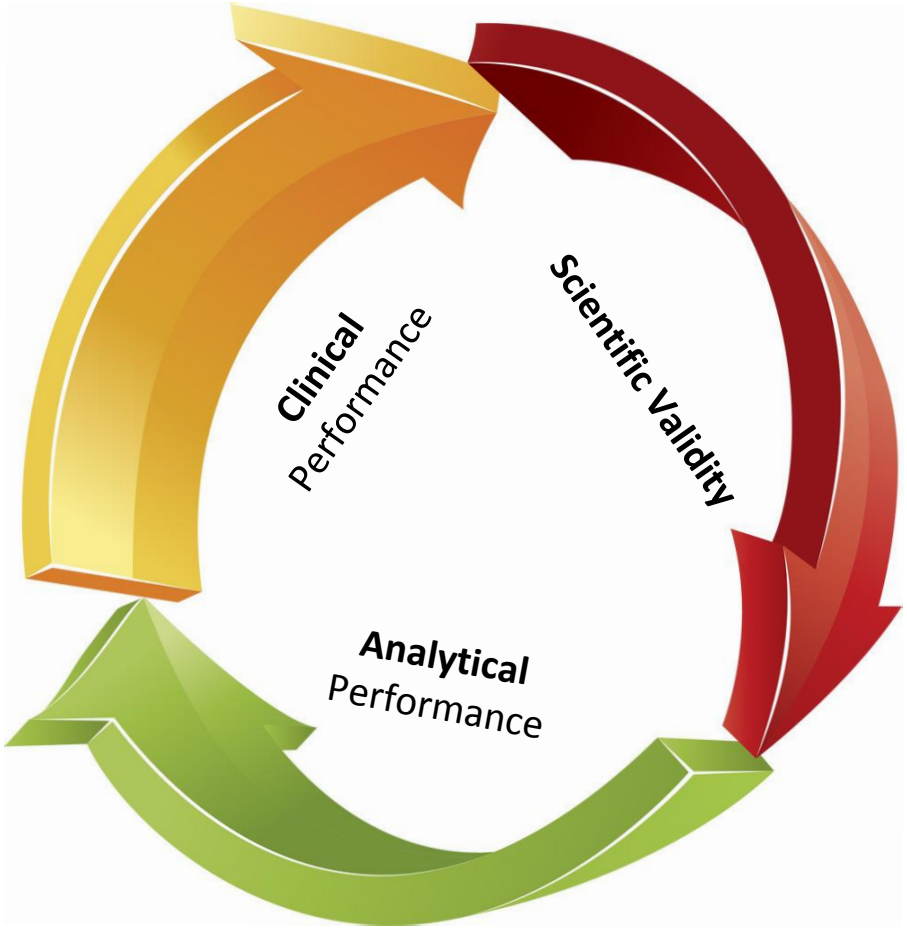

Clinical evidence
Scientific validity
Refers to the association of an analyte to a clinical condition or physiological state
Analytical performance
Refers to the ability of an IVD medical device to correctly detect and measure a particular analyte
Clinical performance
Ability to yield results that relate to a particular clinical condition or physiological state for the intended use and in accordance with target population, and where applicable to the intended user
For established analytes, this may be from literature; but for companion diagnostics or novel analytes this needs to be established
Performance requirements similar to IVD Directive essential requirements
Data to support diagnostic accuracy compared to reference test; information related to expected values

# Performance Evaluation

- Sum total = **Clinical Evidence**
- ***Process*** of Performance Evaluation
- Done according to a **Performance Evaluation Plan**
- Collated as a **Performance Evaluation Report**
- Continuous during life-time of the device

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# Expectations for Performance

**Performance Evaluation Plan**, as well as a file of Clinical Evidence will form part of the Technical Documentation, as a **Performance Evaluation Report**

- **Clinical Performance studies** may be required, unless justified

**Interventional performance studies** – new requirements

- In line with clinical trial expectations for clinical trials of medicinal products

**Clinical Evidence** will need to be updated

- Consolidated text states if there has been a 'trigger', then the PE Report will need updating

**Post-market Surveillance** and **Post-market Performance Follow-up (PMPF)**

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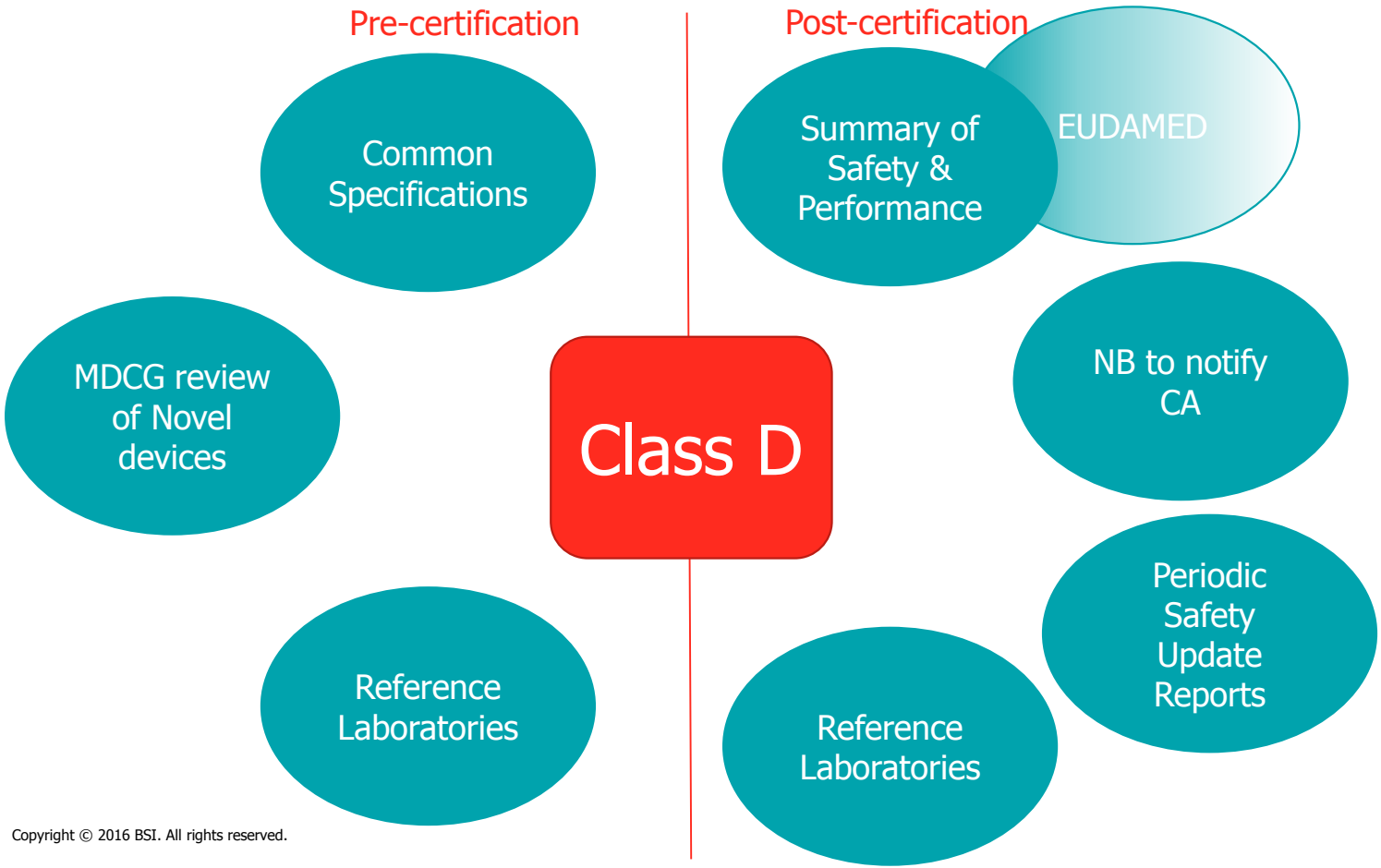
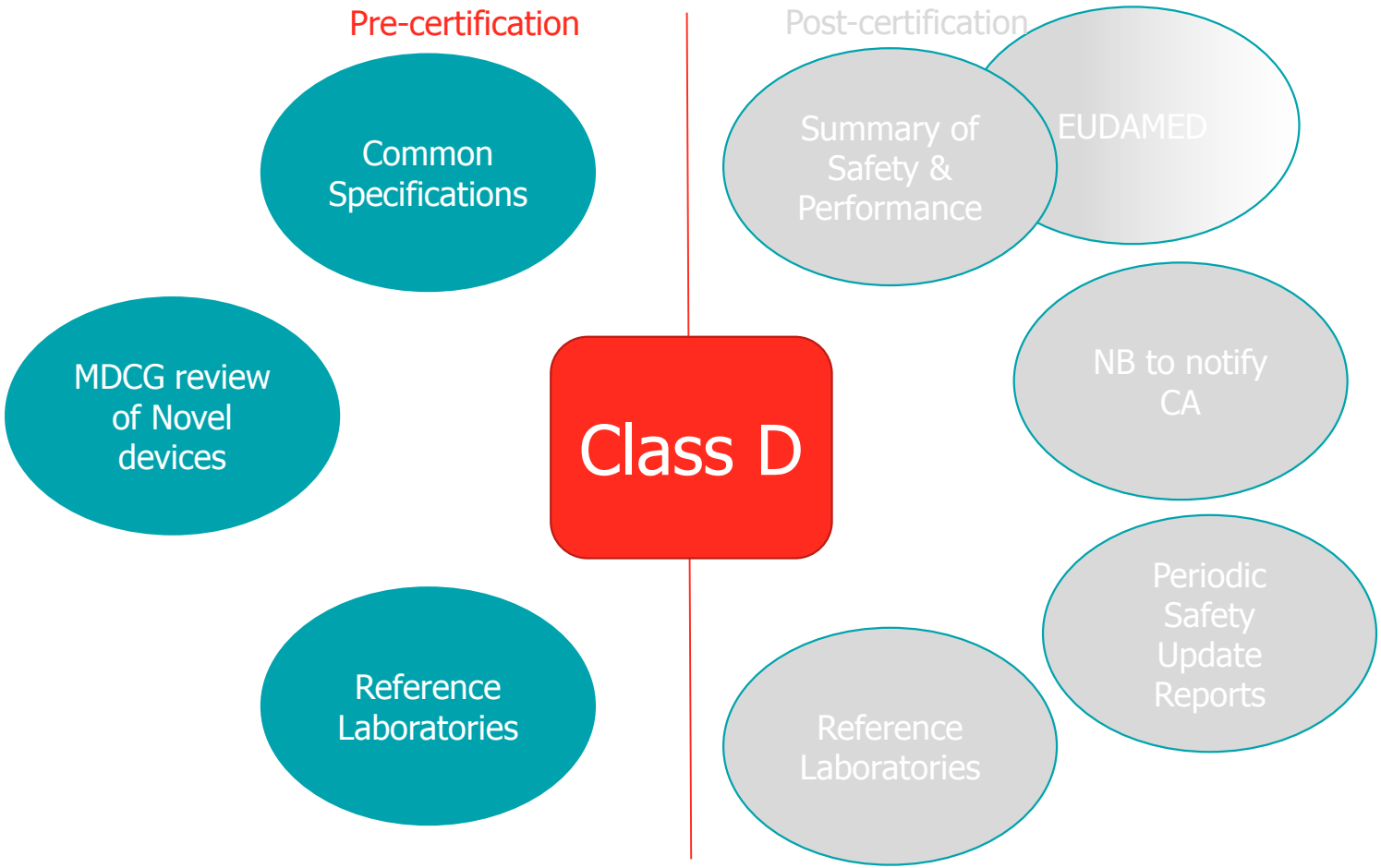
# 6. Scrutiny

# Additional scrutiny of High Risk devices




Pre-certification
Post-certification
Common Specifications
Summary of Safety & Performance
EUDAMED
MDCG review of Novel devices
Class D
NB to notify CA
Periodic Safety Update Reports
Reference Laboratories
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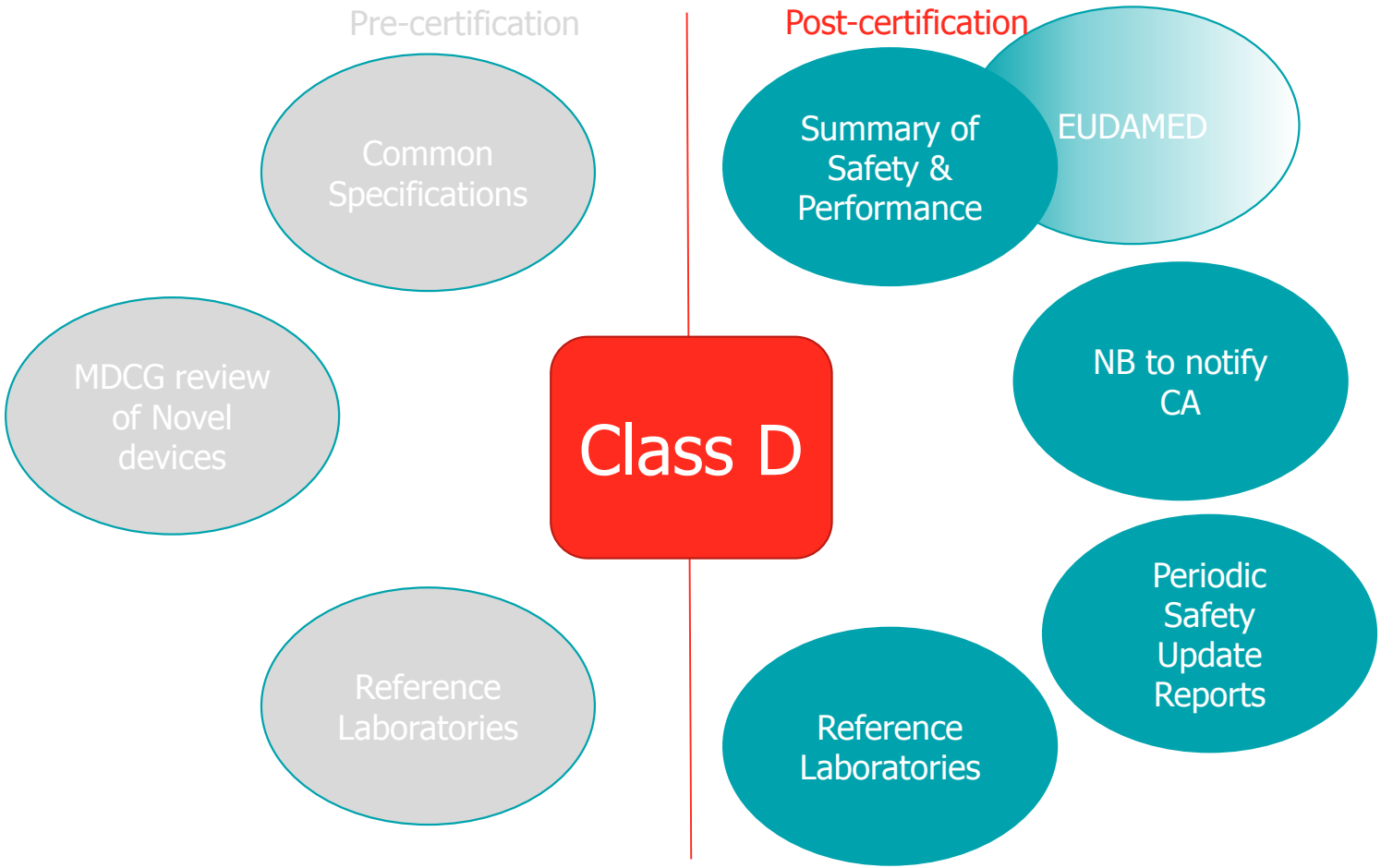
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# 7. Post-market

# Post-market obligations

- **Vigilance** requirements
  - Incident Reporting
  - Trending
- **Post-market Surveillance Plan & Post-market Surveillance**
  - Reviewed as part of Surveillance visits
  - Post-market surveillance Report (Class A & B); or
  - Periodic Safety Update Reports (Class C & D)
- **Post-market Performance Follow-up (PMPF)**
- For Class C & D devices, updates to the **Summary of Safety and Performance**, at least annually
  - Will be publicly available

# Certificates issued under Annex VIII - *surveillance*

## Class C

- EU Quality Management System certificate (Annex VIII, sec 3 & 4)
- Substantial changes
  - Potential audit or assessment
  - Supplement to EU QMS certificate
- Annual surveillance audits
  - Inc Post-market Surveillance Plan
- Unannounced on-site audits, at least every 5 years
- Sampling of technical documentation

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## Class D & Others specified*

- EU Quality Management System certificate (Annex VIII, sec 3 & 4)
- Surveillance as per C (without sampling)
- EU Technical Documentation Assessment certificate (Annex VIII, sec 5 or 6)
- Significant device changes
  - Potential conformity assessment or supplement to EU Tech Doc Assessment certificate
  - Possible Ref Lab consultation if changes impact compliance with the Common Specification (Class D)
- On-going verification of manufactured batches (Class D)

*Self-test and near patient tests, Classed B-D; Companion Diagnostics

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# 8. Companion diagnostics

# Definition

## Companion Diagnostic

means a device which is essential for the safe and effective use of a corresponding medicinal product to:

- identify, before and/or during treatment, patients who are most likely to benefit from the corresponding medicinal product; or

- identify, before and/or during treatment, patients likely to be at increased risk for serious adverse reactions as a result of treatment with the corresponding medicinal product;

# IVDR, Annex VIII 6.2

## Examination of the design of companion diagnostics

a) Manufacturer applies to Notified Body for examination of technical documentation

b) Documentation to enable assessment of conformity with the IVDD

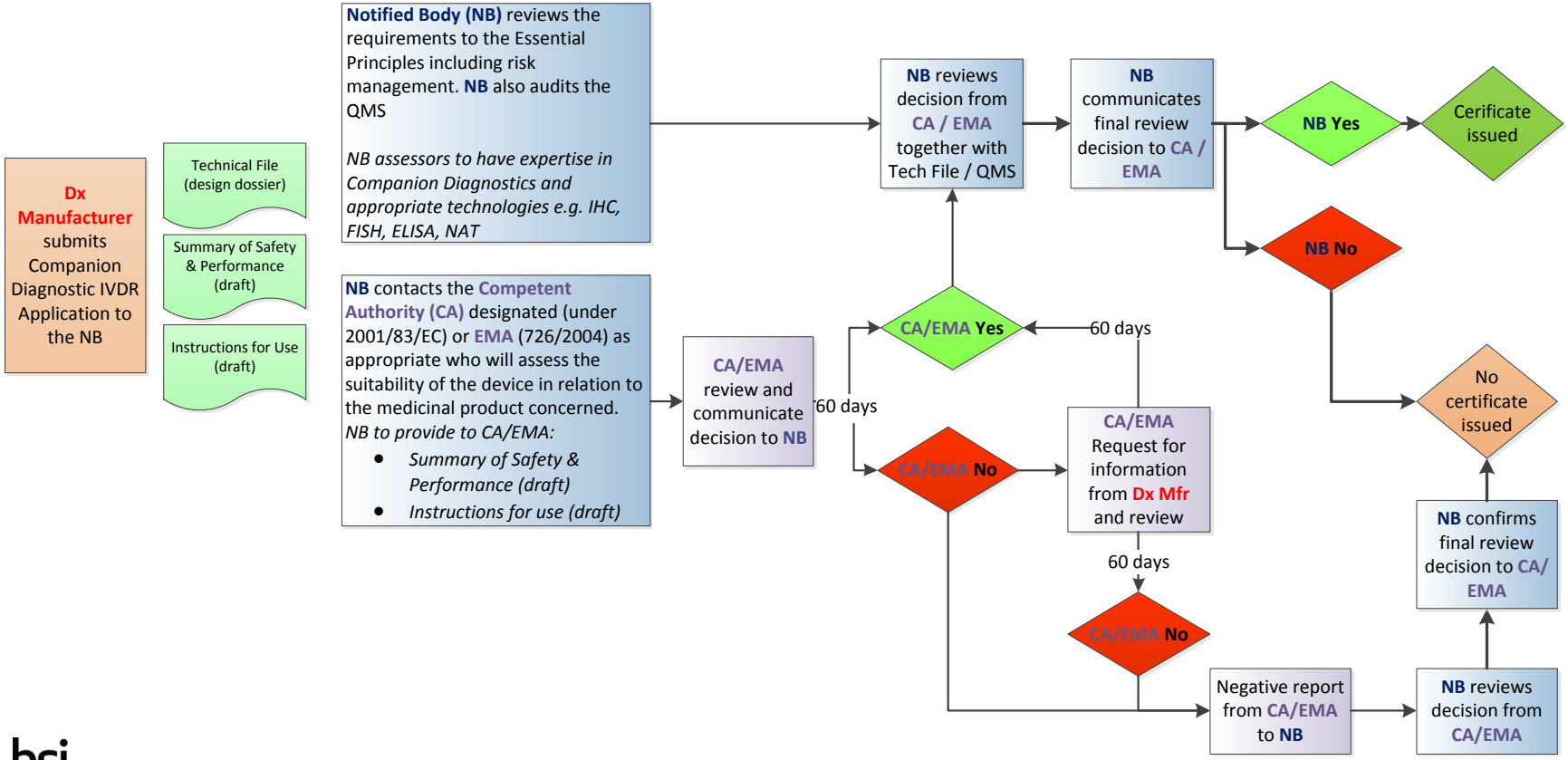
c) Notified body consults with the European Medicines Agency (EMA) or country competent authority (CA)

d) EMA or CA gives opinion to the Notified Body within 60 days

e) Notified body gives due consideration to EMA/CA input

f) Manufacturer to notify the Notified Body of changes. Notified Body determines if a new assessment is needed. Notified Body seeks EMA/CA input

# NB / Drug Competent Authority consultation



# Open questions with CDx conformity assessments

- Which medicinal product Competent Authority will the Notified Body consult?
- Guidance on expectations of medicinal product CA and NB in the review
- IVDR text is based on parallel co-development of test and drug – 'real life' is not necessarily like this
- Will there be a Common Specification?

# 9. In-house Manufacture

Equivalent to “LDT”

# Exemption conditions:

With the **exception of the relevant general safety and performance requirements set out in Annex I**, the requirements of this Regulation shall not apply to devices manufactured and used only within health institutions **established in the Union**, provided that the following conditions are met:

- (aa) the device is **not transferred** to another legal entity,
- (a) manufacture and use of the device occur under appropriate **quality management systems**,
- (b) the laboratory of the health institution is **compliant with standard EN ISO 15189** or where applicable national provisions, including national provisions regarding accreditation.
- (c) the health institution justifies in its documentation that the target patient group's **specific needs cannot be met** or cannot be met at the appropriate level of performance by an equivalent device available on the market,

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'health institution' means
an organisation whose primary purpose is the care or treatment of patients or the promotion of public health;

Devices that are manufactured and used within health institutions shall be considered as being put into service.

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# Exemption conditions:

- (d) the health institution provides information upon request on the use of such devices to their **competent authority**, which shall include a justification of their manufacturing, modification and use;

- (e) the health institution **draws up a declaration**, that it shall make **publicly available**, including:
  - the name and address of the manufacturing health institution;
  - the details necessary to identify the devices;
  - a declaration that the devices meet the general safety and performance requirements set out in Annex I of this Regulation and, where applicable, information on which requirements are not fully met with reasoned justification,

# Exemption conditions:

(f) as regards devices classified as **class D** in accordance with the rules set out in Annex VII, the health institution draws up documentation,

- allowing an understanding of the manufacturing facility,
- the manufacturing process,
- the design and performance data of the devices, including the intended purpose, sufficiently detailed to enable the competent authority to ascertain that the general safety and performance requirements set out in Annex I of this Regulation are met.

**Member States may apply this provision also to devices classified as class A, B and C** in accordance with the rules set out in Annex VII;

# Exemption conditions:

(g) the health institution takes all necessary measures to ensure that all devices are manufactured in accordance with the documentation referred to in point (f), and

(h) the health institution **reviews experience gained from clinical use** of the devices and takes all necessary corrective actions.

- Member States may require that the health institutions submit to the competent authority any further relevant information about such devices which have been manufactured and used on their territory.
- Member States shall retain the **right to restrict the manufacture** and use of any specific type of such devices and shall be permitted access to inspect the activities of the health institutions.

These **provisions do not apply to devices which are manufactured on an industrial scale**.

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# 10. Other aspects of significant impact

# Other significant impacts

- New General Safety and Performance requirements
- Requirements and increased scrutiny of Notified Bodies
- Increased obligations of Economic Operators
    - Inc. Authorised Representatives, Importers, Distributors
- Person Responsible for Regulatory Compliance
    - Manufacturers (or Auth Rep) with Degree + 1 yr IVD experience; or 4 yrs IVD experience
- UDI and device registration
    - Impact on labelling; phased in under the IVDR
- Requirements for interventional performance studies (or studies with risks to subjects)
- Reference Laboratories
- Vigilance

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# 10. What now…

# What now…

## Notified Bodies

- Preparing themselves for designation
- NBOG codes will be needed

## Manufacturers

- Project Plan according to current texts
- Engage with your/a Notified Body
- Use the Transition Period effectively!

## Other Economic Operators

- Authorised Representatives, Importers and Distributors need to plan to meet new obligations

# Useful links

- Current IVDD
  - http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CONSLEG:1998L0079:20090807:EN:PDF
- European Commission Recommendation on Unannounced Audits
  - http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2013:253:0027:0035:EN:PDF
- Index of MEDDEV Guidance Documents
  - http://ec.europa.eu/growth/sectors/medical-devices/guidance/index_en.htm
- European Commission Medical Device Landing Page
  - http://ec.europa.eu/growth/sectors/medical-devices/index_en.htm
- Draft IVDR
  - http://data.consilium.europa.eu/doc/document/ST-10618-2016-INIT/en/pdf
- GHTF Archives
  - http://www.imdrf.org/ghtf/ghtf-archived-docs.asp
- BSI IVD Resources
  - http://medicaldevices.bsigroup.com/en-GB/technologies/ivd/
- BSI Webinars
  - www.bsigroup.com/en-GB/medical-devices/resources/webinars/