Pathways to IVDR Compliance – IVD Extended Webinar

25 April 2023

Presented by Alex Laan and Elizabeth Harrison

Key IVDR Updates…why and when

Alex Laan
Head IVD Notified Body– IVD devices, BSI

Key IVDR Updates…why and when

1. EU IVDR developments
   - Transitional Provisions Amendment 2022/112
   - Amendment March 2023 to Article 110 IVDR
   - MDCG 2022-6 and MDCG 2022-14
2. EU Notified Body status
3. Questions and Answers

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IVDR Amendment EU 2022/112

28.1.2022 EN Official Journal of the European Union L 19/3

REGULATION (EU) 2022/112 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

of 25 January 2022

amending Regulation (EU) 2017/746 as regards transitional provisions for certain *in vitro* diagnostic medical devices and the deferred application of conditions for in-house devices

(Text with EEA relevance)

THE EUROPEAN PARLIAMENT AND THE COUNCIL OF THE EUROPEAN UNION,

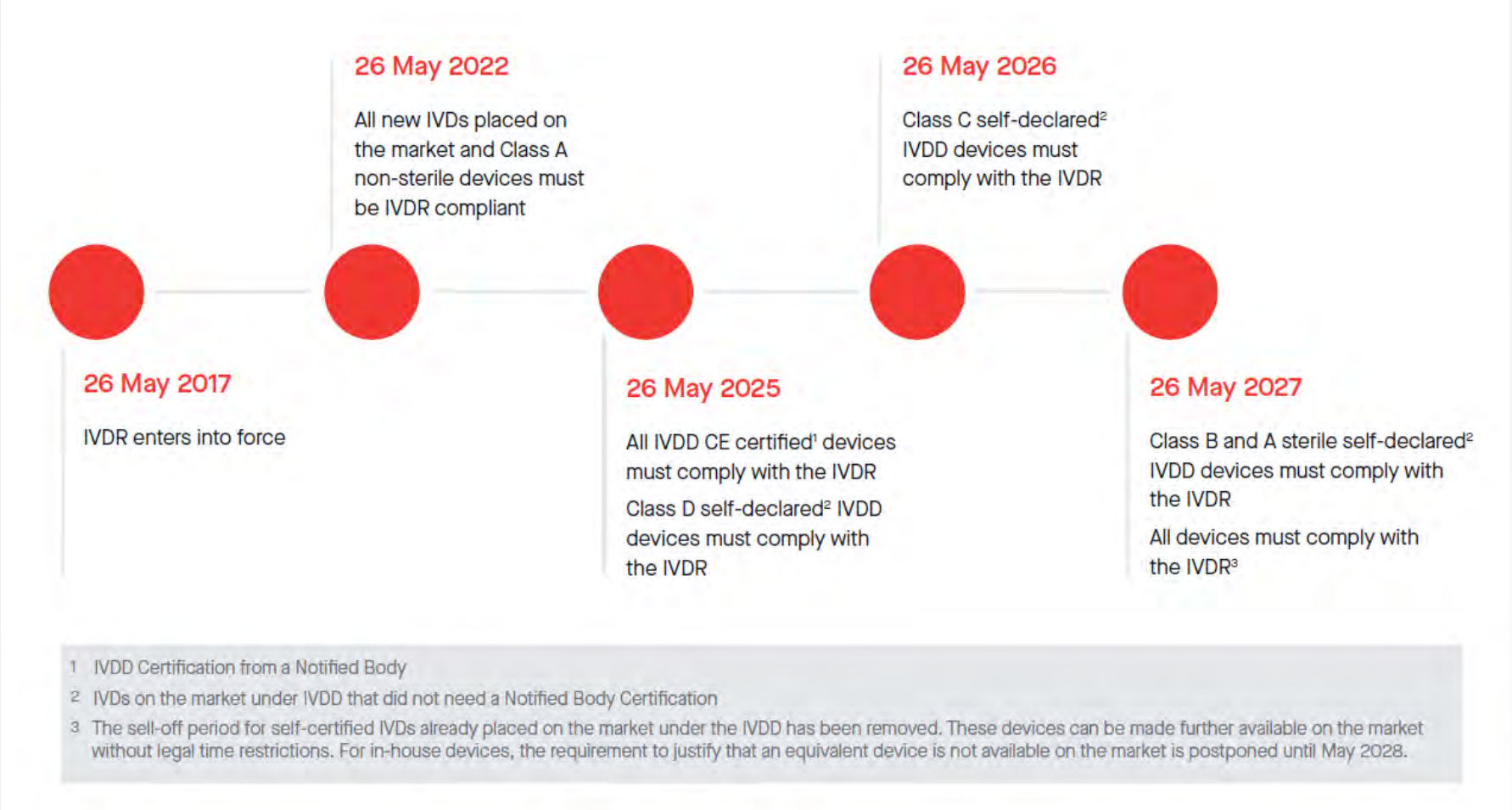
Having regard to the Treaty on the Functioning of the European Union, and in particular Article 114 and Article 168(4), point (c), thereof,

Having regard to the proposal from the European Commission,

After transmission of the draft legislative act to the national parliaments

Transitional Provisions extended per (EU) 2022/112

https://eur-lex.europa.eu/eli/reg/2022/112/oj/eng



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MDR & IVDR Amendment (another)

L 80/24 EN Official Journal of the European Union 20.3.2023

REGULATION (EU) 2023/607 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

of 15 March 2023

amending Regulations (EU) 2017/745 and (EU) 2017/746 as regards the transitional provisions for certain medical devices and *in vitro* diagnostic medical devices

(Text with EEA relevance)

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Having regard to the Treaty on the Functioning of the European Union, and in particular Article 114 and Article 168(4), point (c), thereof,

Having regard to the proposal from the European Commission,

After transmission of the draft legislative act to the national parliaments,

Having regard to the opinion of the European Economic and Social Committee ([1]),

EPSCO meeting December 2023 and it's impact on IVDR / Notified Body

- New Commission amendment for a Regulation of the European Parliament and of the Council amending Regulations (EU) 2017/745 and (EU) 2017/746; 2023/607 as regards the transitional provisions for certain medical devices and *in vitro* diagnostic medical devices. The amendment Regulation, that has been adopted by the European Parliament and the Council, aims at introducing a staggered extension of the transition period provided for in Regulation (EU) 2017/745 on medical devices (MDR), subject to certain conditions. It also aims at deleting in both MDR and IVDR the 'sell-off' deadline after which devices placed on the market before or during the transition periods that are still in the supply chain would have to be withdrawn.
- Important to understand that this amendment mostly affects MDR.

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EPSCO meeting December 2023 and it's impact on IVDR / Notified Body / MDCG 2022-18 resulting in Regulation 2023/607

Legislative amendment changes:

- Staggered and conditional extension of the transition period until 2027/2028, according to risk class of the device (MDR only).
- "Extended validity" of certificates (MDR only).
- Cancellation of "sell-off" date i.e., allowing devices placed on the market before or during the transition period to continue to be made available without time limitation.
- Bridging measures based on application of market surveillance provisions (MDR only).
- Gaining momentum to increase number of notified bodies
- Implementation of actions to enhance notified body capacity and ensure availability of medical devices and in vitro diagnostics, as agreed by the Medical Device Coordination Group

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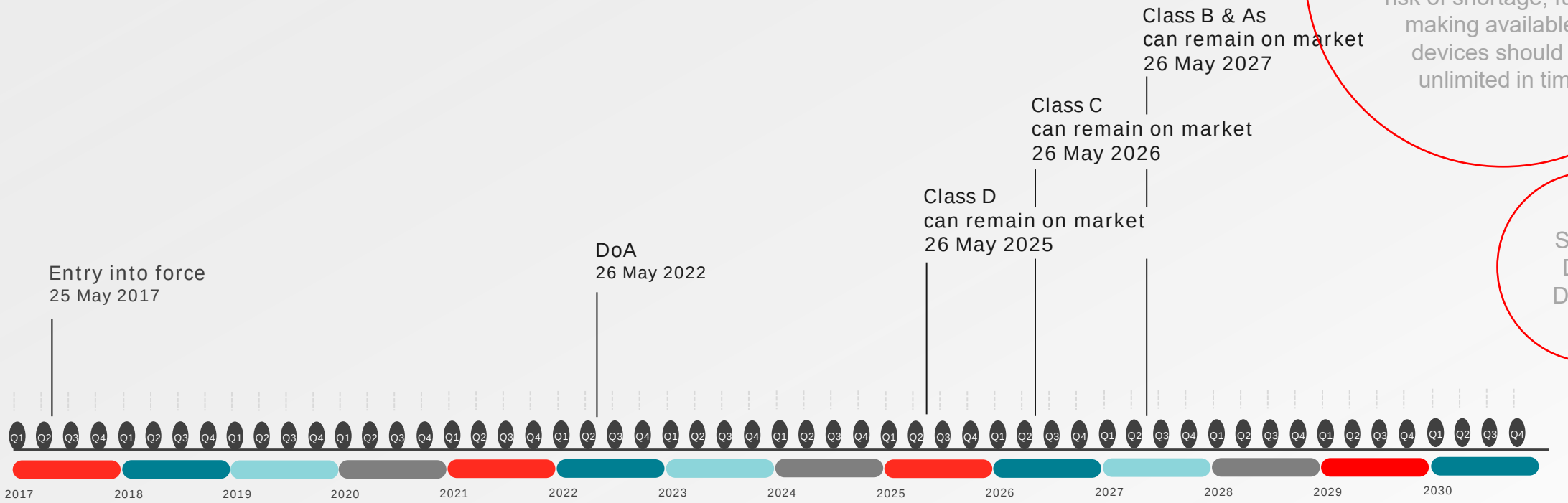
What – Proposed IVDR Transition?

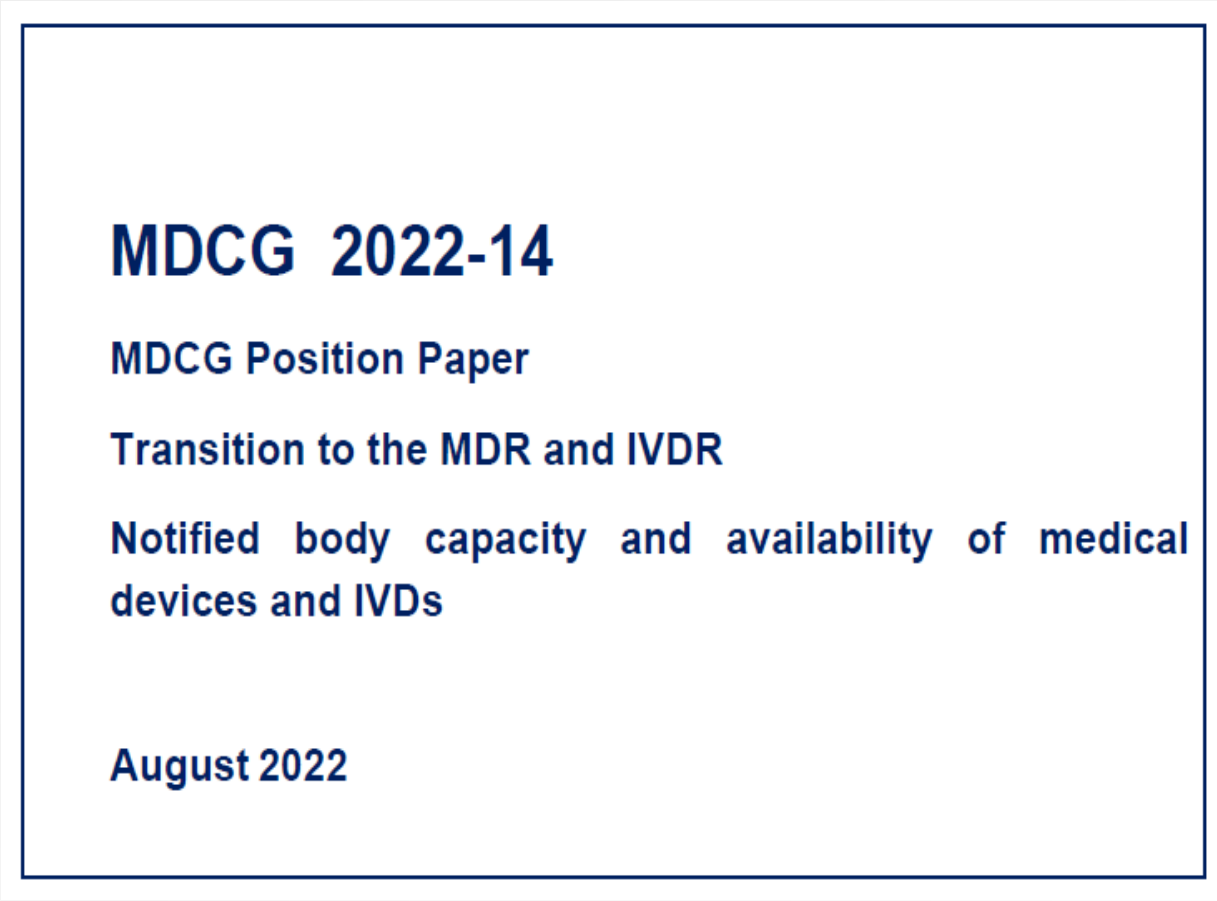


'to prevent unnecessary disposal of safe MD & IVD that are still in the supply chain, thus adding to the imminent risk of shortage, further making available of devices should be unlimited in time'

Sell Off Dates Deleted

Specific actions from MDCG 2022-14

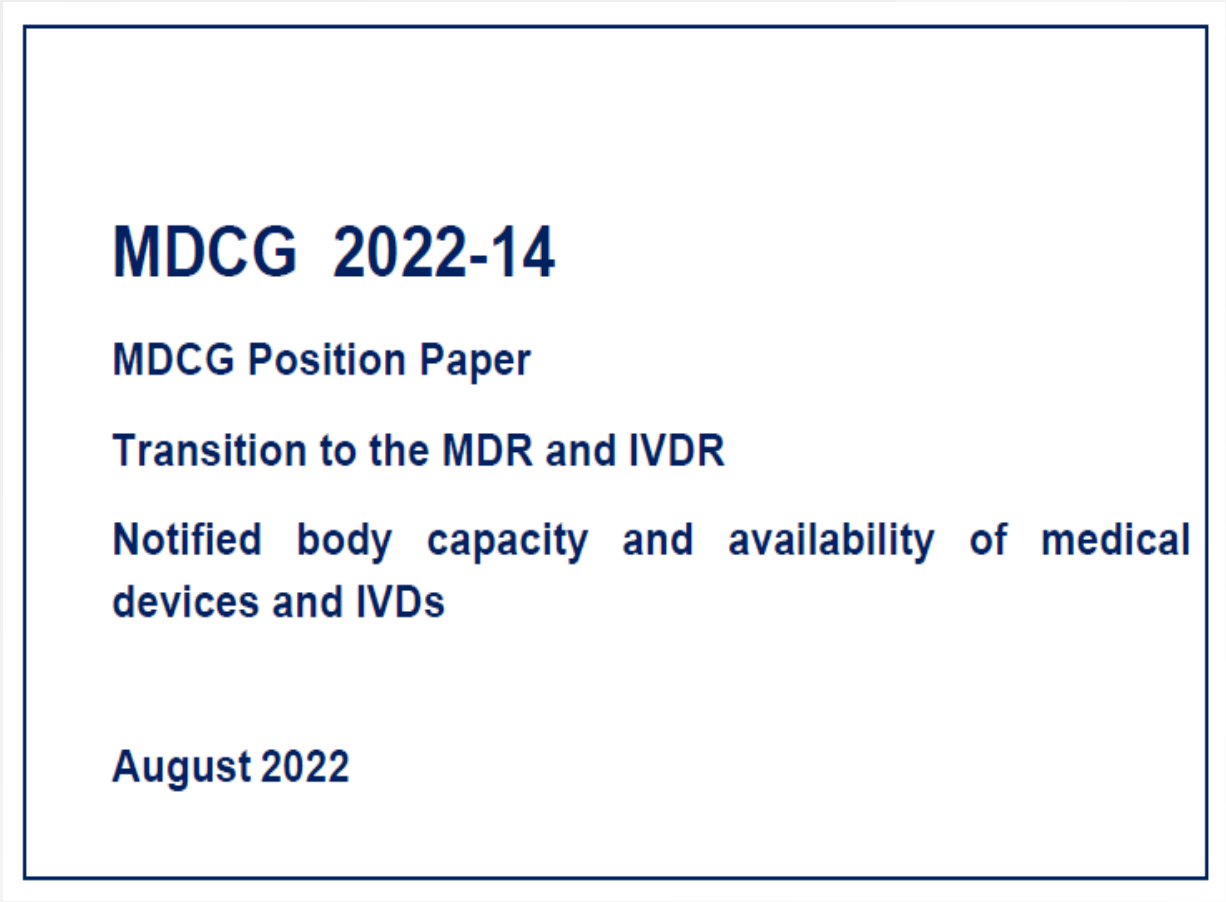
- The document focuses mostly on the issues causing capacity constraints and limited access towards Notified Bodies.
- It summarises a total of 16 points dealing with the Notified Body constraints and 3 additional points dealing with other actions facilitating transition to MDR / IVDR and avoiding shortage of devices.
- General text contains “soft language”; “encourages”, “should”, “can make”, not really a document that supports a strong enforcement. But, a step in the right direction.



Specific actions from MDCG 2022-14

Most important actions that Notified Bodies are going to undertake:

- Implementation of Hybrid Audits
- Opportunities for leveraging evidence from previous assessments (for instance Annex II List A and List B)
- Extend IVDR codes for re-designation, where warranted
- Appropriate surveillance of legacy devices (IVDD)
- Allocate capacity for SME manufacturers and first-time applicants
- Organize "structured dialogues"
- Provide training to increase the preparedness of manufacturers, especially SME's and first time applicants



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MDCG 2022-6 - Significant Changes **under Article 110**

Non-significant change

Changes to the device that:

- **are not essential to the device's operating principle**
- **do not adversely affect the safety or performance**
- **do not negatively affect the risk/benefit ratio**

✓ changes of the Legal MFR name, address or legal form, including merger or acquisition;

✓ relocation or addition of new manufacturing sites, including subcontractors or suppliers;

✓ restricting the target population, specimen type, specimen location;

✓ changes in incubation times and temperatures; changes in the processing steps of the method (e.g. a new washing step);

✓ substitution of a chemical substance in order to comply with the REACH Regulation (EC) No 1907/2006;

✓ extension or reduction of shelf life of a non-sterile device;

✓ change of instructions for use to refer to better precision of the device based on data obtained as a result of post-market surveillance;

✓ clarifications of labelling or instructions for use.

Significant change

Changes to the device that:

- **alter the device's operating principle**
- **adversely affect the safety or performance**
- **negatively affect the risk/benefit ratio**

✓ change of instructions for use to refer to reduced sensitivity of the device based on data obtained as a result of post-market surveillance;

✓ alteration of assay-specific cut-off values resulting in decreased specificity;

✓ change of assay type, e.g. from screening assay to confirmatory assay or from qualitative to quantitative assay;

✓ substitution of a chemical substance in order to comply with the REACH regulation with an adverse impact on performance of the device.

Operating principle: *the overall assay or testing method(s), mechanism(s) or principle(s) of measurement, including the detection principle, which the device uses to achieve its intended purpose, (e.g. enzyme-linked immunosorbent assay (ELISA) with chemiluminescence-based detection, polymerase chain reaction (PCR), isothermal DNA amplification)*

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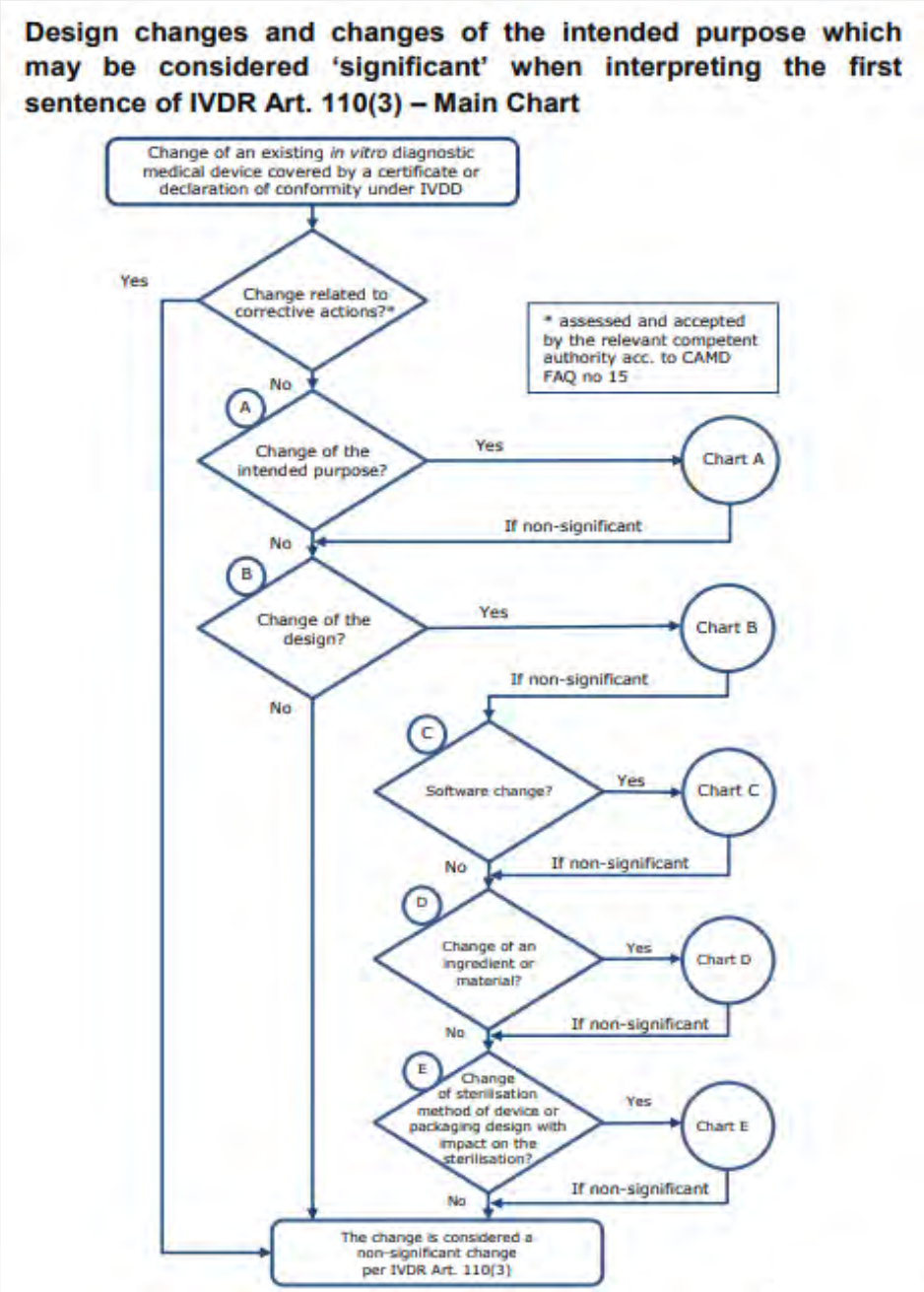
Significant Changes **under Article 110**

MDCG 2022-6

Outlines:

- Examples of non-significant changes
- **Flow charts** in Annex
- Annex A: Change of intended purpose
- Annex B-E: Change in design
- **Not all changes in design or intended purpose are 'significant'** (case by case)
  - In general: **Corrective actions for field safety** are *not* regarded as 'significant'
  - Correction of spellings/typos in IFU – not significant
  - Updates to labelling by other laws (that do not change risk) [eg CLP]



MDCG: Dec 2022 – Jan 2023

Reference	Title	Publication Date
MDCG 2022-17	MDCG position paper on "hybrid audits"	12/2022
MDCG 2022-18	MDCG Position Paper on the application of Article 97 MDR to legacy devices for which the MDD or AIMDD certificate expires before the issuance of a MDR certificate	12/2022
MDCG 2022-19	Performance study application/notification documents under Regulation (EU) 2017/746	12/2022
MDCG 2022-20	Substantial modification of performance study under Regulation (EU) 2017/746	12/2022
MDCG 2022-21	Guidance on Periodic Safety Update Report (PSUR) according to Regulation (EU) 2017/745	12/2022
MDCG 2022-4 rev. 1	Guidance on appropriate surveillance regarding MDR Art.120 transitional provisions - devices covered by MDD or AIMDD certificates	12/2022
Manual on Borderline	Manual on borderline and classification under Regulations (EU) 2017/745 and 2017/746 – Version 2	12/2022

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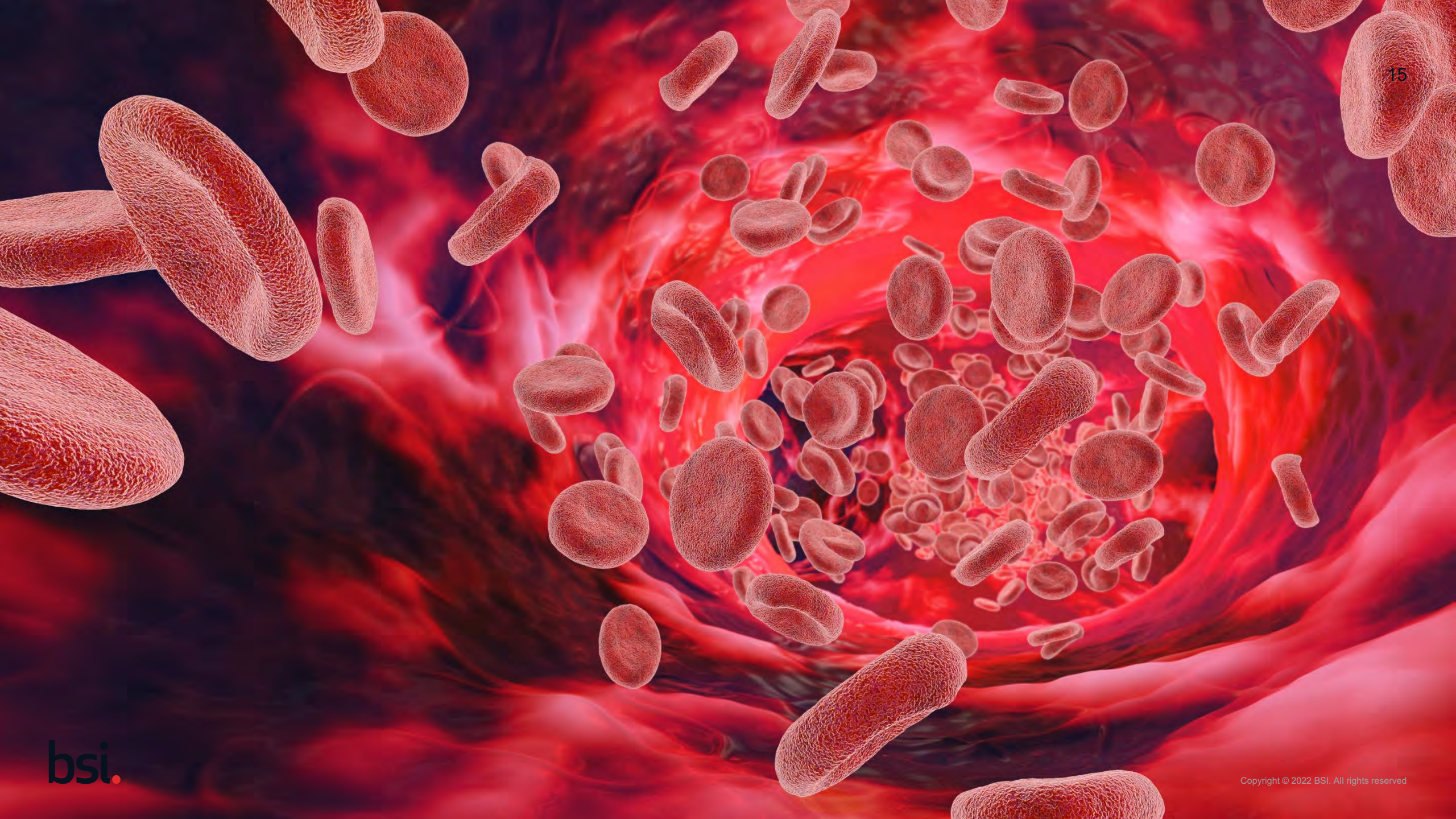

IVDR Notified Bodies – current status

IVDD Notified Bodies, n=19

Body type	Name	Country
NB 2265	3EC International a.s.	Slovakia
NB 2797	BSI Group The Netherlands B.V.	Netherlands
NB 2409	CE Certiso Orvos- és Kórháztechnikai Ellenőrző és Tanúsító Kft.	Hungary
NB 0318	CENTRO NACIONAL DE CERTIFICACION DE PRODUCTOS SANITARIOS	Spain
NB 2934	CeCert Sp. z o.o.	Poland
NB 0344	DEKRA Certification B.V.	Netherlands
NB 1293	EVPU a.s.	Slovakia
NB 0537	Eurofins Electric & Electronics Finland Oy	Finland
NB 0459	GMED SAS	France
NB 1023	INSTITUT PRO TESTOVÁNI A CERTIFIKACI, a. s. (INSTITUTE FOR TESTING AND CERTIFICATION) merged with ex-NB 1390	Czech Republic
NB 0373	ISTITUTO SUPERIORE DI SANITA'	Italy
NB 0483	MDC MEDICAL DEVICE CERTIFICATION GMBH	Germany
NB 1011	NEOEMKI Nemzeti Orvostechnikai Eszköz Megfelelőségértékelő és Tanúsító Korlátolt Felelősségű Társaság (NEOEMKI LLC)	Hungary
NB 0050	National Standards Authority of Ireland (NSAI)	Ireland
NB 1434	POLSKIE CENTRUM BADAN I CERTYFIKACJI S.A.	Poland
NB 0543	Presafe Denmark A/S	Denmark
NB 0197	TÜV Rheinland LGA Products GmbH	Germany
NB 0123	TÜV SÜD Product Service GmbH	Germany
NB 2854	bqs. s.r.o.	Slovakia

IVDR Notified Bodies, n=10

Body type	Name	Country
NB 2265	3EC International a.s.	Slovakia
NB 2797	BSI Group The Netherlands B.V.	Netherlands
NB 0344	DEKRA Certification B.V.	Netherlands
NB 0124	DEKRA Certification GmbH	Germany
NB 0459	GMED SAS	France
NB 0483	MDC MEDICAL DEVICE CERTIFICATION GMBH	Germany
NB 0050	National Standards Authority of Ireland (NSAI)	Ireland
NB 2962	QMD Services GmbH	Austria
NB 0197	TÜV Rheinland LGA Products GmbH	Germany
NB 0123	TÜV SÜD Product Service GmbH	Germany

source: Nando (14th March 2023)

IVDR Notified Bodies – current status

Notified Bodies Survey on certifications and applica
(MDR
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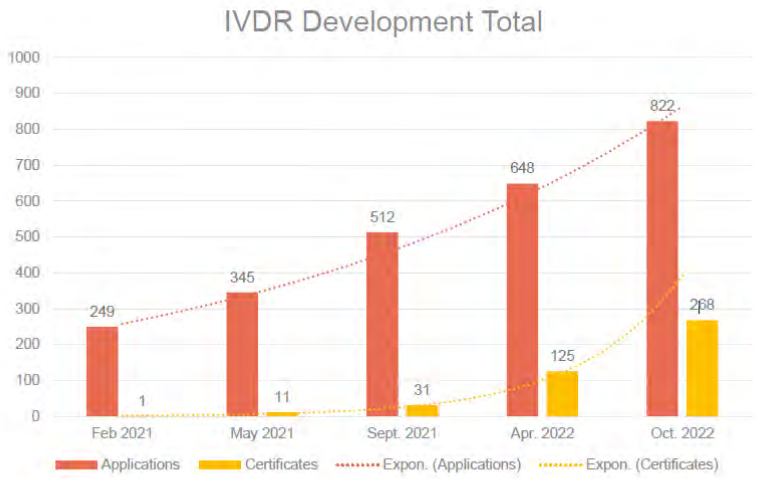
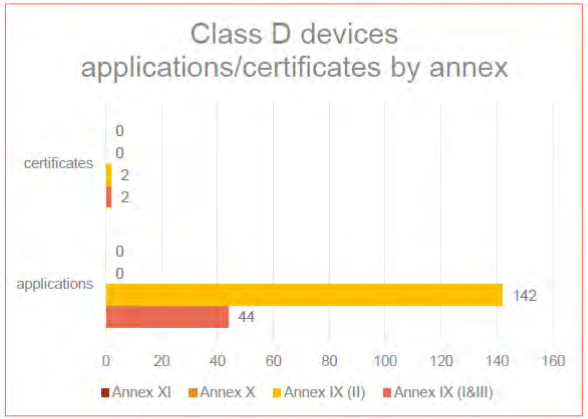
IVD

Survey on certifications and applications

IVDR Applications and Certificates

IVDR Data (1/5)





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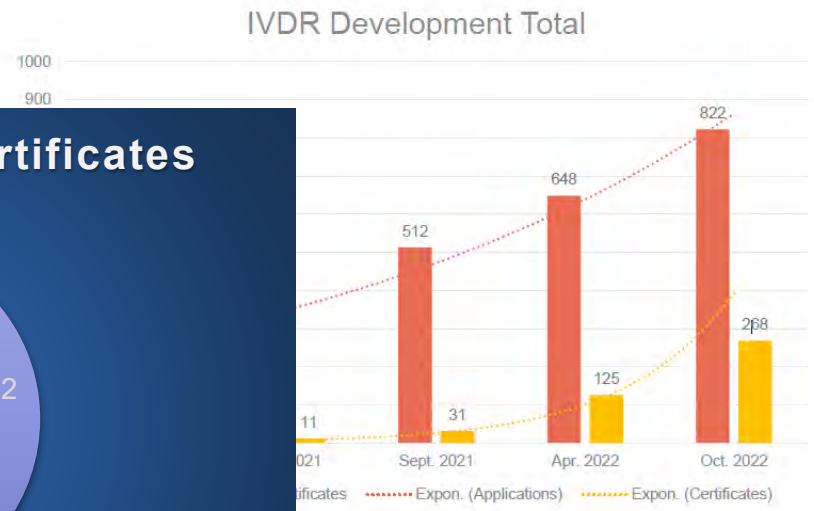
European Commission

Notified Bodies Survey on certifications and a

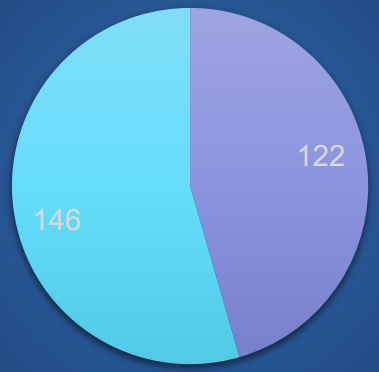
IVD

Survey on certifications and applications

IVDR Applications and Certificates

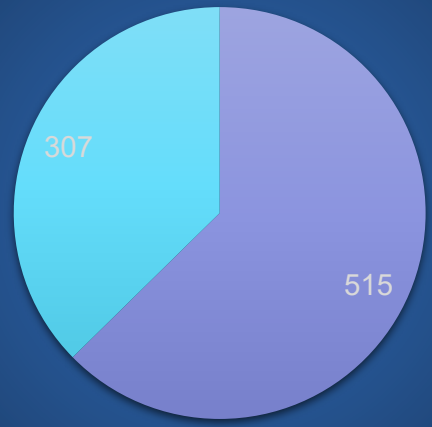


Total issued IVDR certificates



BSI certificates Other NBs

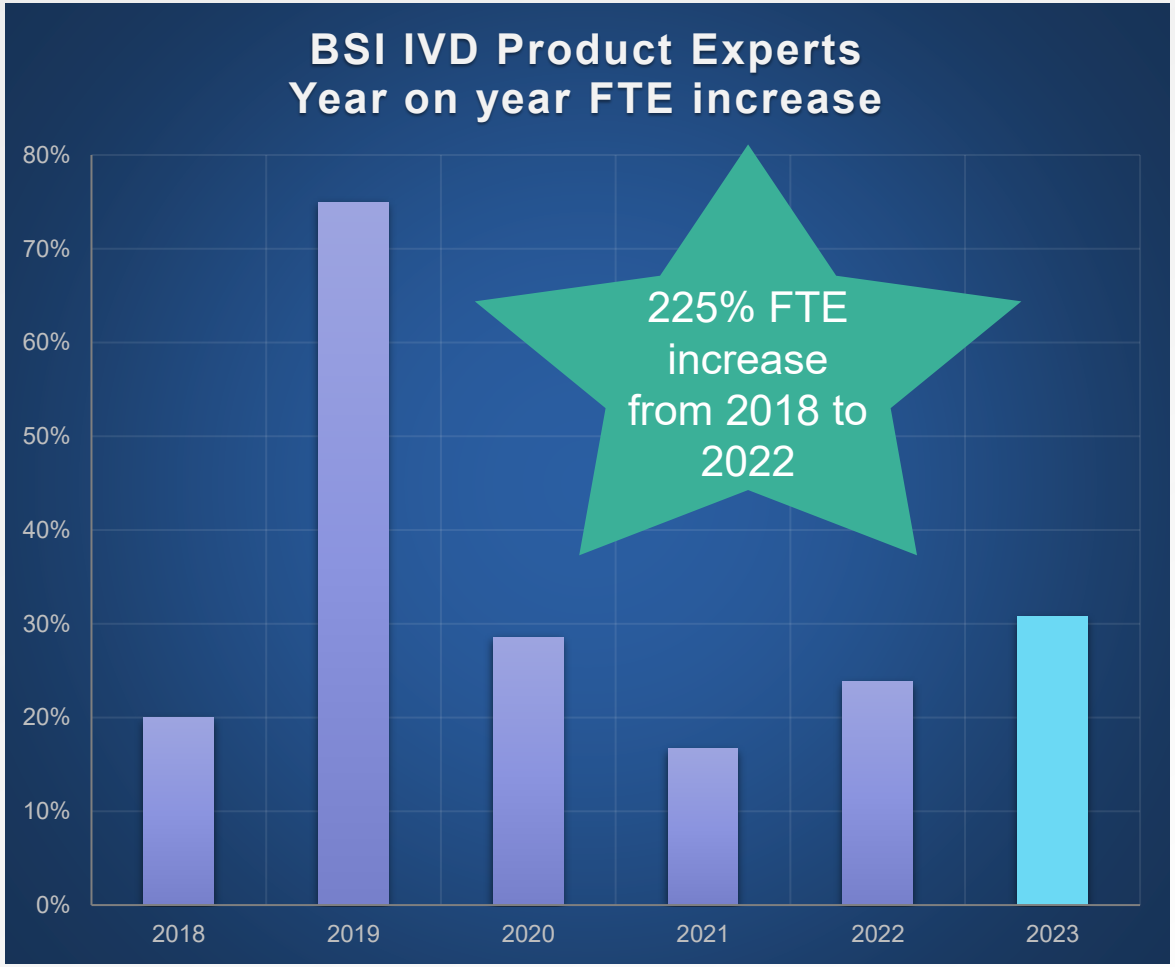
Total IVDR applications



BSI Applications Other NBs

IVDR Notified Body Capacity

BSI IVDR journey	
2010	IVDD designation
2014	First IVDR product expert hire
2017	IVDR Entry into force
Dec 2019	IVDR designation
Jun 2020	IVDR applications ramp up
Dec 2020	First BSI IVDR certificate issued
Jan 2022	IVDR transition change published
May 2022	IVDR Date of Application
Jan 2023	First BSI Class D certificates issued
?? 2023	*First BSI CDx certificates issued…*



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IVDR Current Status – Final Comments…

New to market devices struggling for NB resource among the devices transitioning from IVDD

New amendments have been published that will give manufacturers (and notified bodies) more time to implement.

Transition extension feels generous…BUT! …

Do not assume NBs will have capacity for your device type closer to the deadlines!

Engage with a Notified Body early – it takes longer than you think!

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Guidance

MDCG Endorsed Documents:

https://health.ec.europa.eu/medical-devices-sector/new-regulations/guidance-mdcg-endorsed-documents-and-other-guidance_en

BSI IVD website:

https://www.bsigroup.com/en-GB/medical-devices/our-services/IVDR-Revision/

- Webinars
- Whitepapers
- Training Courses

Telling a Story

Creating effective technical documentation

Liz Harrison
Global Head - IVD

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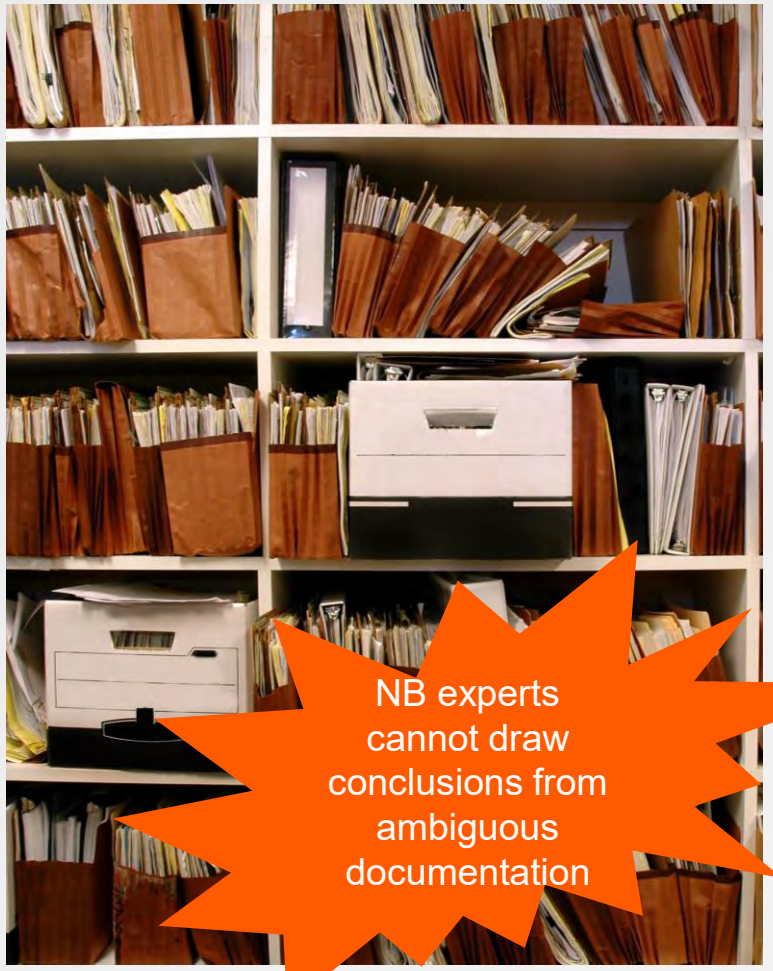
Technical Documentation – Requirements



A complete and well-organized file decreases NB review time and your costs.

Annex II & III

"to be drawn up by the manufacturer shall be presented in a clear, organised, readily searchable and unambiguous manner and shall include in particular the elements listed in this Annex"

Annex II 4. (d) – GSPR Checklist

"precise identity"

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Article 10 – General obligations of manufacturer

4. Manufacturers shall draw up and keep up to date the technical documentation for those devices. The technical documentation shall be such as to allow the conformity of the device with the requirements of this Regulation to be assessed. The technical documentation shall include the elements set out in Annexes II and III.

Depth and extent of assessment is the **same** for Class B, C and D *MDCG 2019-13*

"depth and extent shall be **proportionate** and appropriate to the characteristics of the device including the risks, risk class, performance and its intended purpose" *(Annex XIII sec 1)*

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Technical Documentation – General considerations

IVDR Document Submissions - Best Practise Guidelines

BSI guidance:

- https://www.bsigroup.com/globalassets/meddev/localfiles/it-it/guidance/bsi-md-ivdr-best-practice-documentation-submissions-it-en.pdf

Notified Body Working Group submission guidance

- https://www.team-nb.org/wp-content/uploads/members/M2023/Team-NB-PositionPaper-BPG-IVDR-V1-20230225.docx

IVDR is very prescriptive

- Gap analysis to cover all elements
- Provide justifications for non-applicability
- Use international standards & guidelines for your implementation

Use IVDR terminology!

- FDA files will not be compliant

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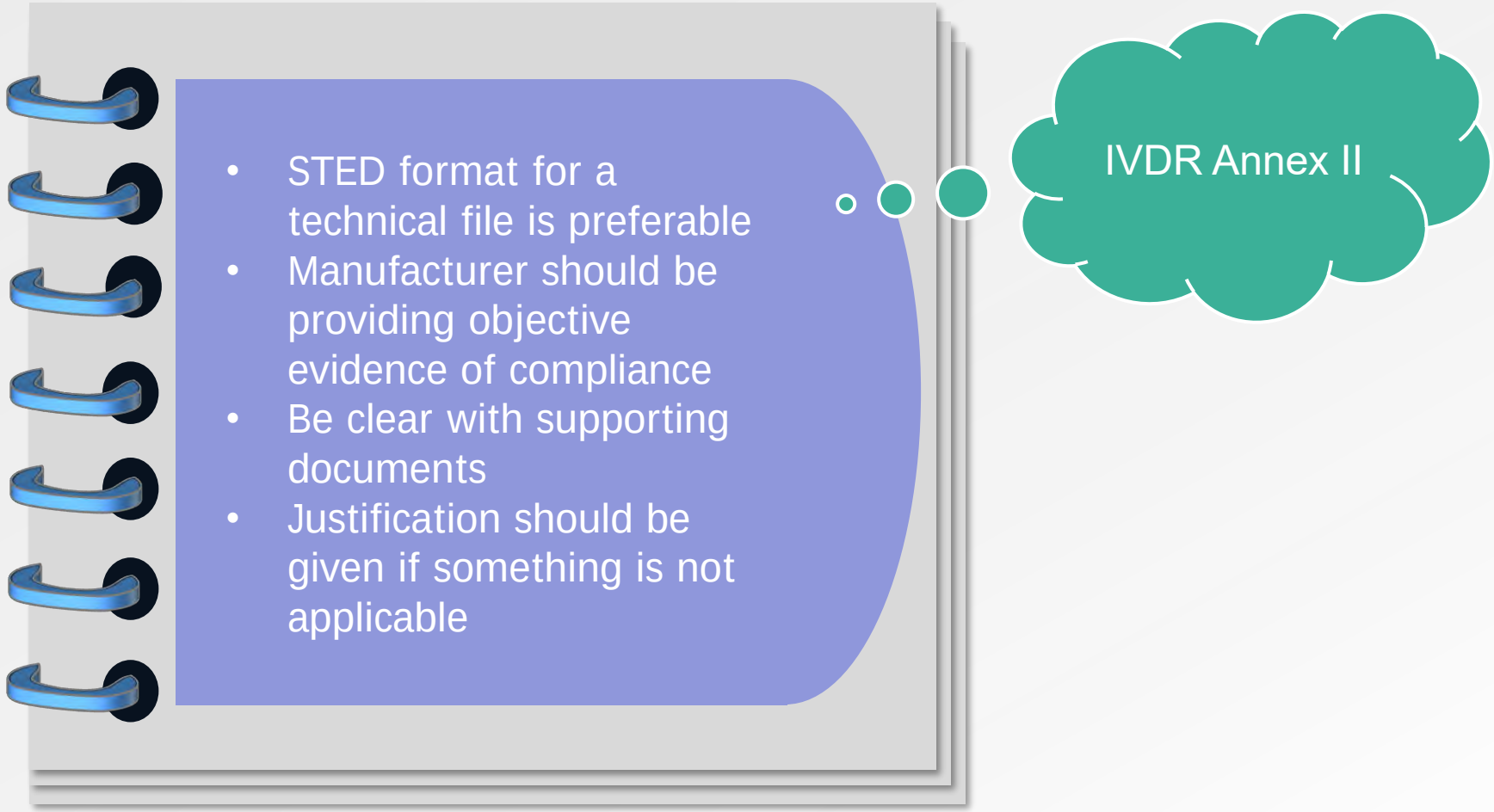
Technical Documentation - Structure / Format



IVDR Annex II ‘Technical Documentation’

1. Device description and specification, including variants and accessories
2. Information to be supplied by the manufacturer
3. Design and manufacturing information
4. General safety and performance requirements
5. Benefit-risk analysis and risk management
6. Product verification and validation

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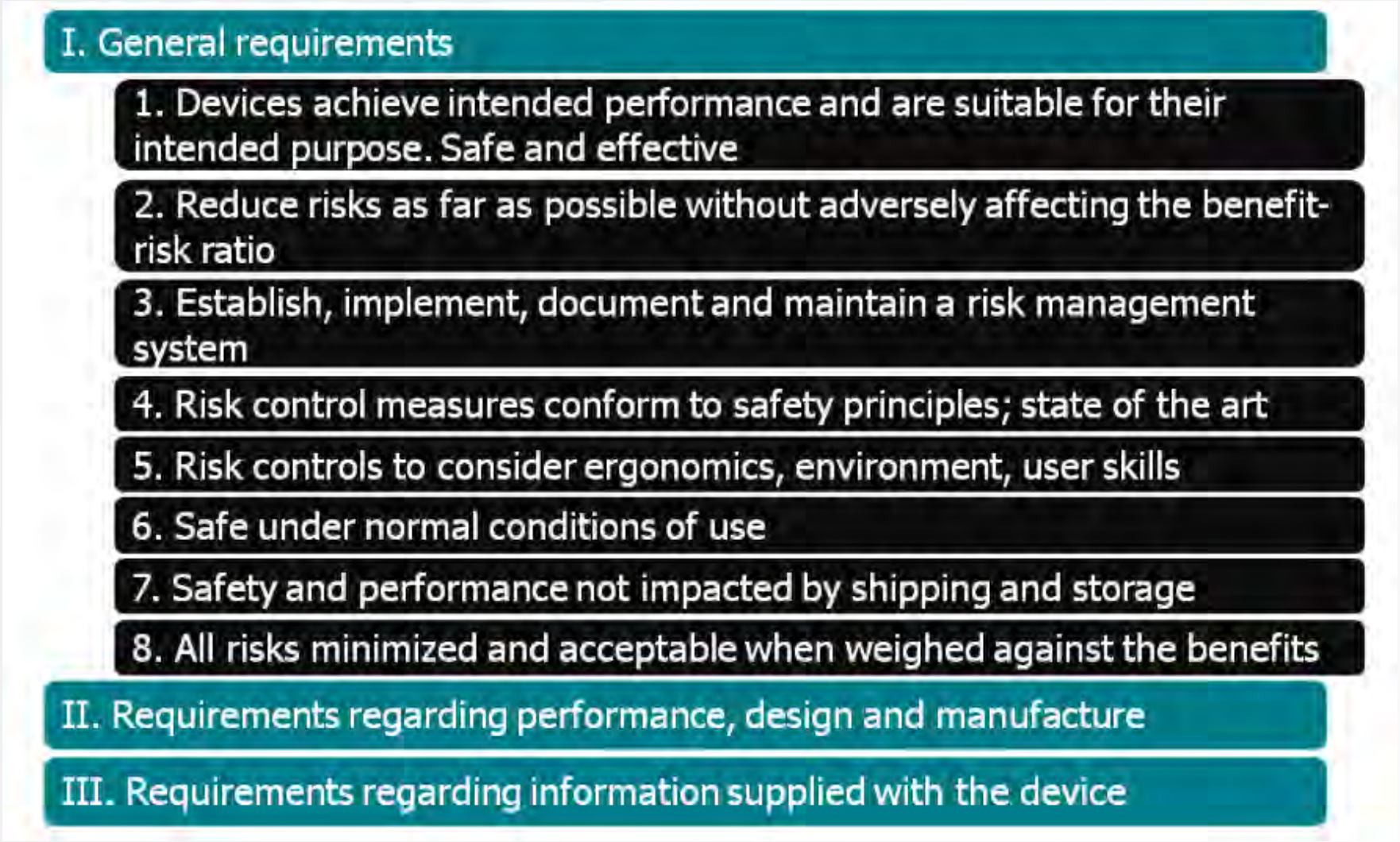
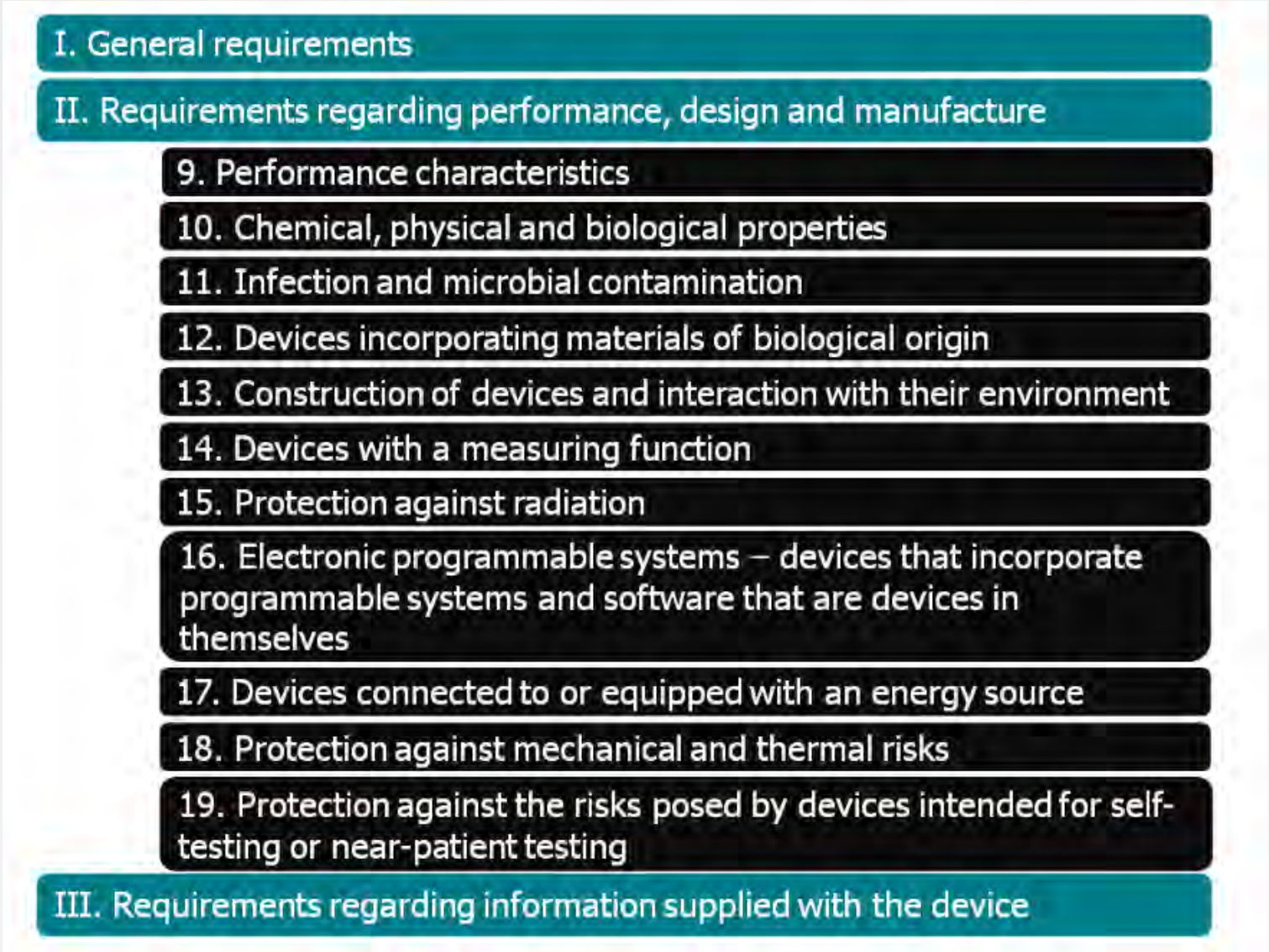
IVDR Annex I ‘General Safety and Performance Requirements (GSPRs)

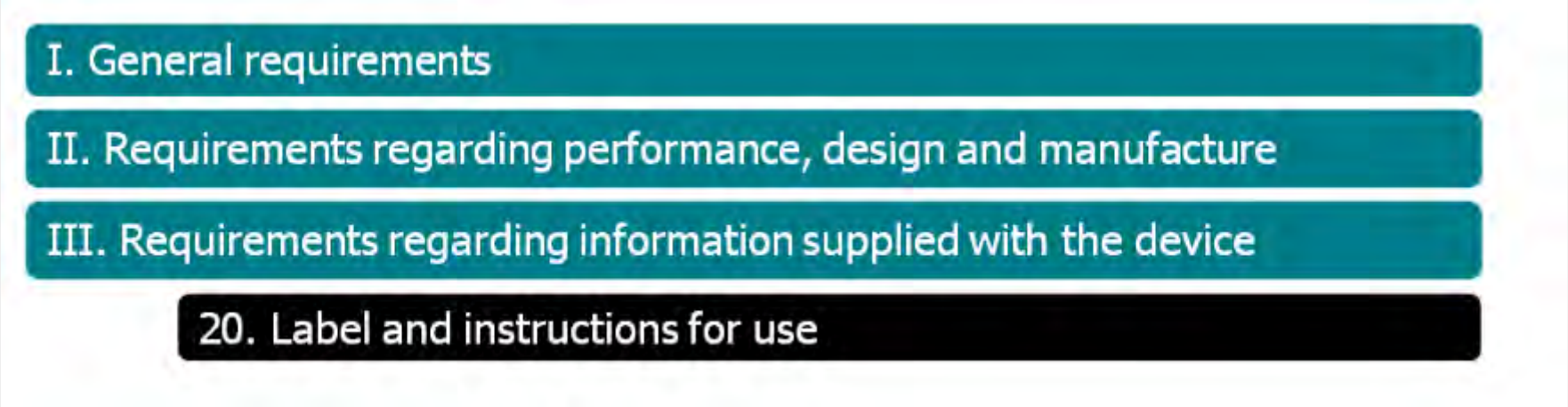
IVDR Annex I - GSPRs



IVDR Annex I - GSPRs



IVDR Annex I - GSPRs



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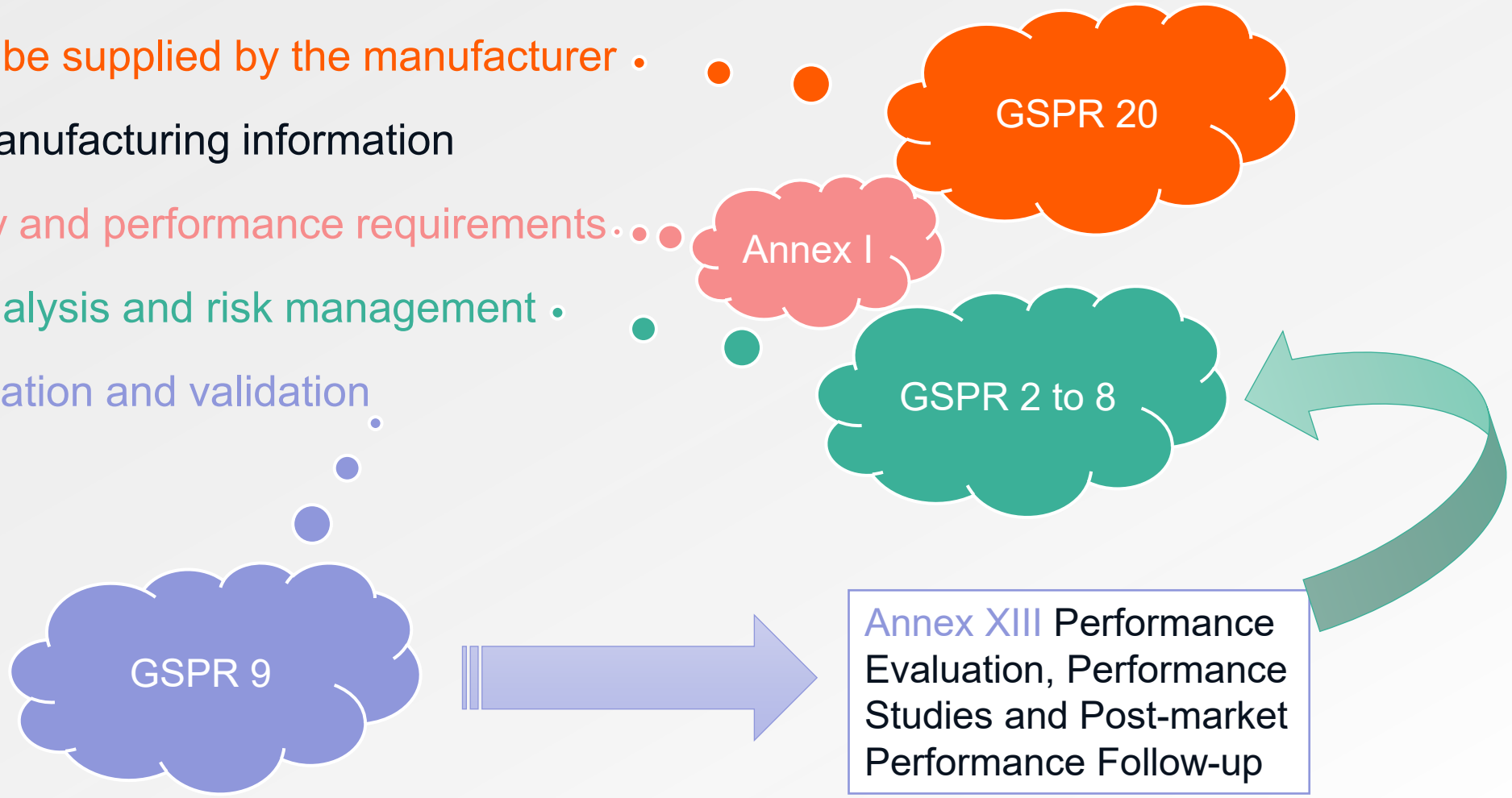

IVDR Annex III ‘Technical Documentation on Post-Market Surveillance’

Requirements:

1. Post-market surveillance plan
2. Post-market performance follow-up (PMPF) plan
3. Periodic safety update report (PSUR)
4. Post-market surveillance report

All device types

Post-market surveillance plan (Article 79)

This should include a PMPF plan, unless justified not applicable

Class A and B

Post-market surveillance report (Article 80)

Class C and D

Periodic safety update report (Article 81)

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IVDR Annex II ‘Technical Documentation’

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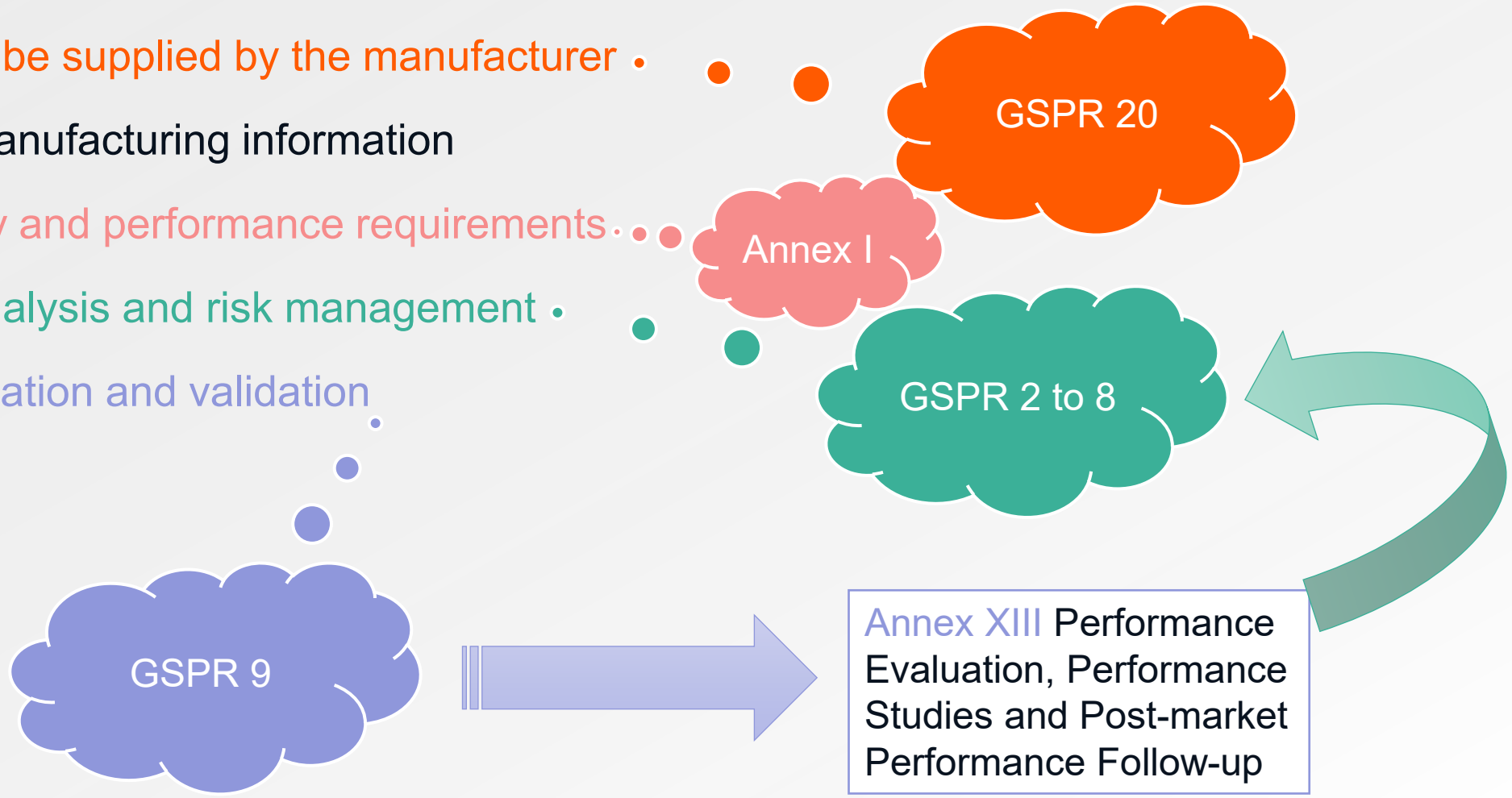

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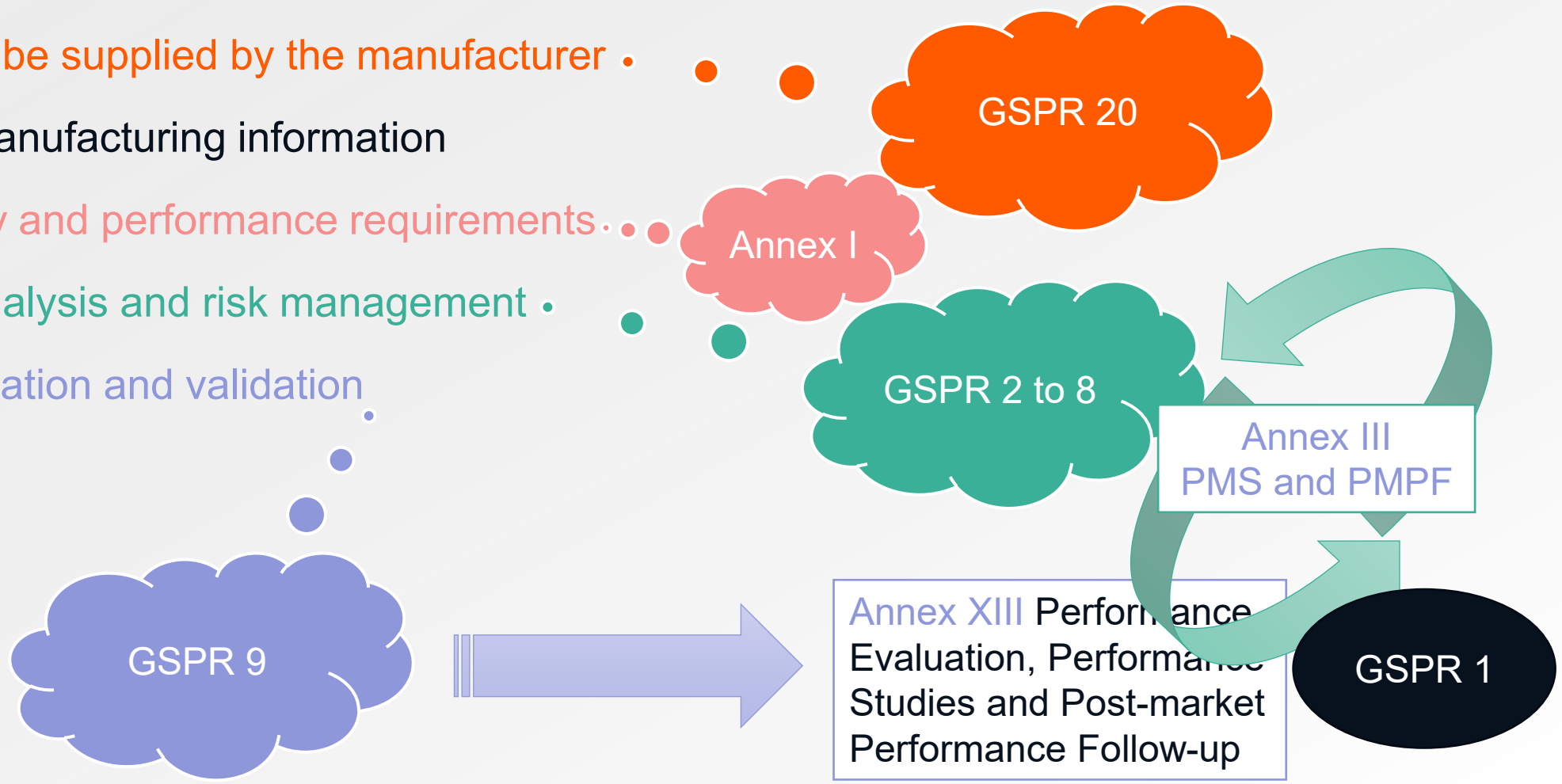

Technical Documentation – Specific considerations

Technical Documentation proportionate to risk class & intended purpose

- ✓**Control or Calibrator?**
- ✓**Software?**
- ✓**Test / assay – NGS assay vs ELISA?**
- ✓**User: *professional - near-patient - self test***

Standalone file for each component or one per system?

Technical Documentation – Accessory vs system approach?

Tip! ***Set the scene, supply appropriate context for a reviewer to understand***

Annex II section 1.1 – Device description and specification

- Include **identification** and **classification** of all accessories, including software

- The Notified Body does not need to review Class A elements

✓ Be clear in the documentation so that the Notified Body reviewer understands the scope of their review

Technical Documentation – Accessory vs system approach?

System approach

Is it clear which requirements and data apply to which accessory or sub system?

- ➢ GSPR 12 *Devices incorporating materials of biological origin*
- ✓ May apply to reagents but not instruments or software
- ➢ GSPR 17 *Devices connected to or equipped with an energy source*
- ✓ May apply to instruments but not reagents

Accessory approach

- ➢ Be clear on the accessory intended purpose and provide evidence to meet that purpose
- ✓ Explain the scope of the evidence included
- ➢ Many requirements are likely to not be applicable
- ✓ Provide robust justifications

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Technical Documentation - Tips

Annex II format is recommended

Annex II section 1:

- ➢ Set the scene
- ✓ Sets the scope of the Notified Body review

Annex III for PMS

Annex XIII for PE *(Annex II section 6)*

Check for consistency

- ➢ Device name
- ➢ Intended Purpose
- ➢ Performance claims

- ✓ Technical documentation
- ✓ IFU
- ✓ Declaration of conformity

Understand linkages between sections

- ➢ Allows documentation to be updated over the product life cycle
- ✓ Meet Notified Body surveillance expectations

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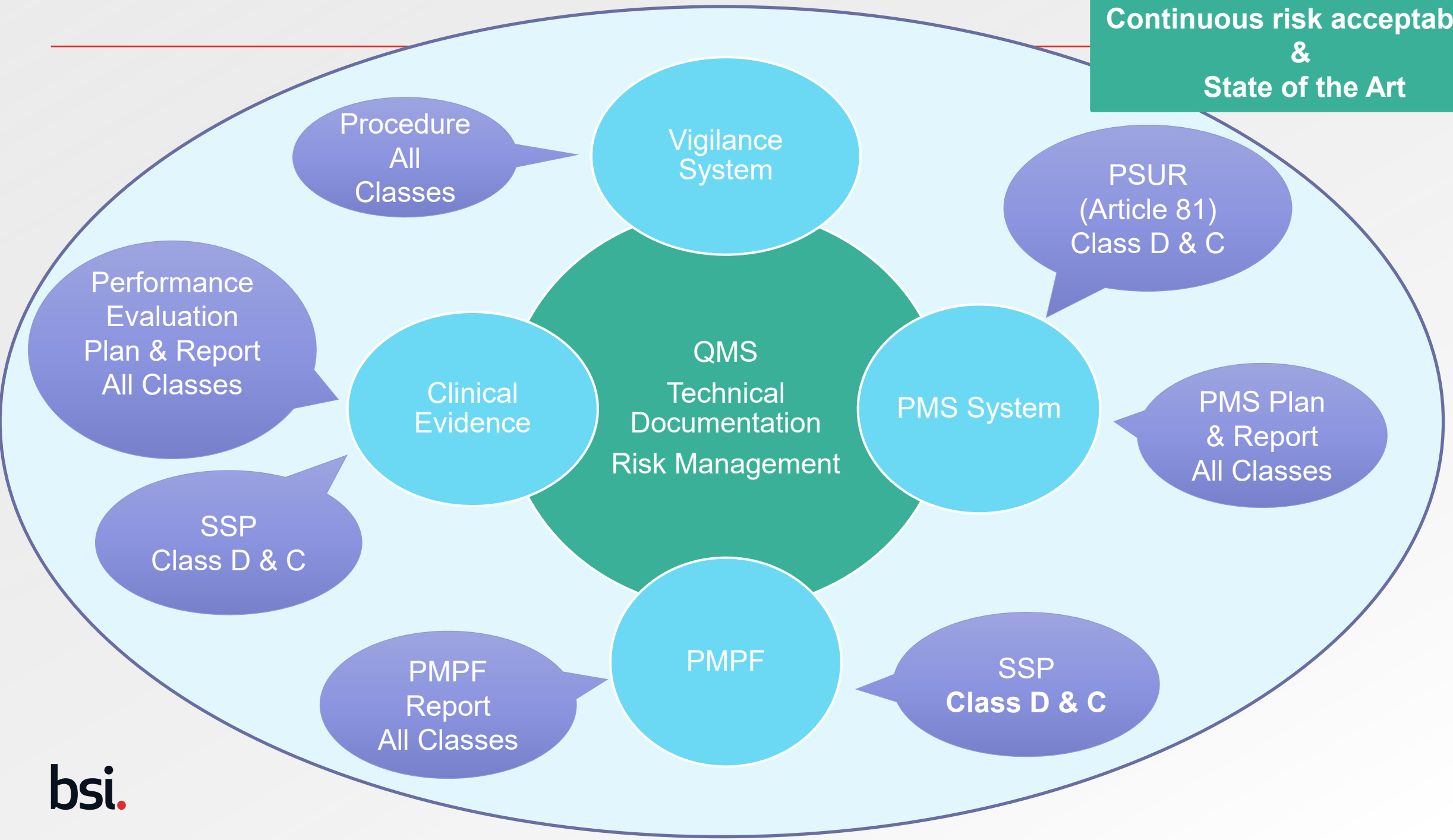
Continuous risk acceptability
&
State of the Art



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Q & A Session

IVDR Clinical Evidence:

Understanding the requirements

Liz Harrison
Global Head - IVD

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Clinical Evidence under the IVDR

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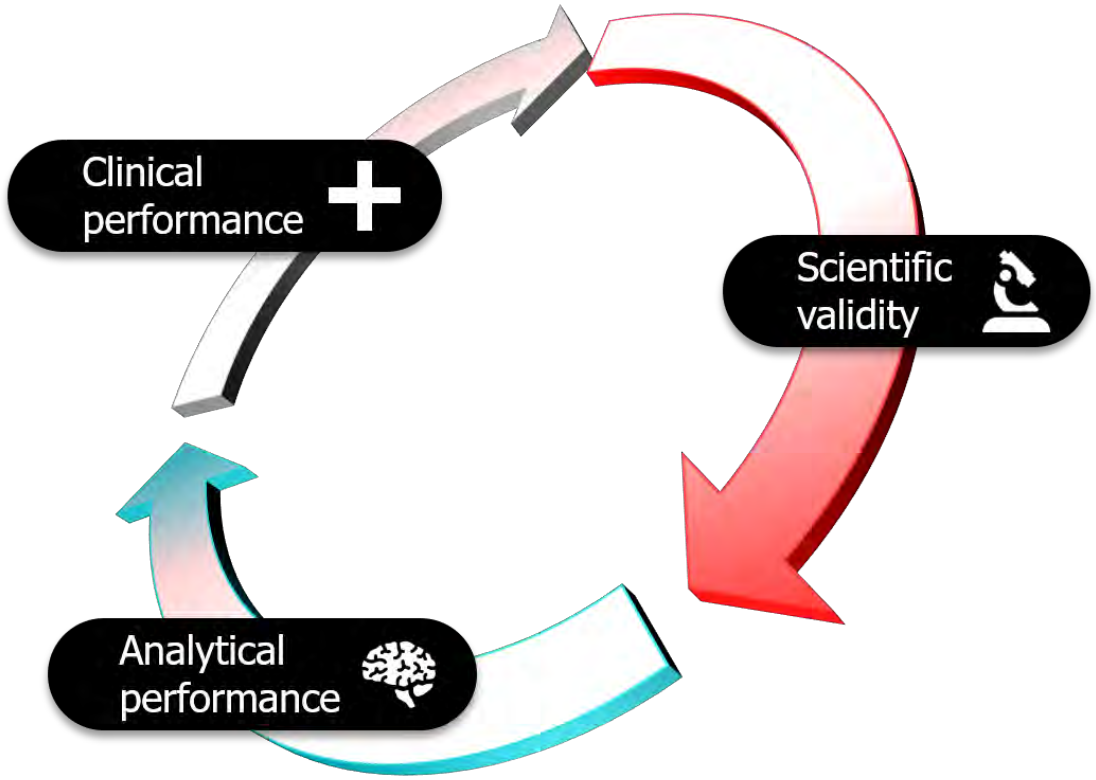
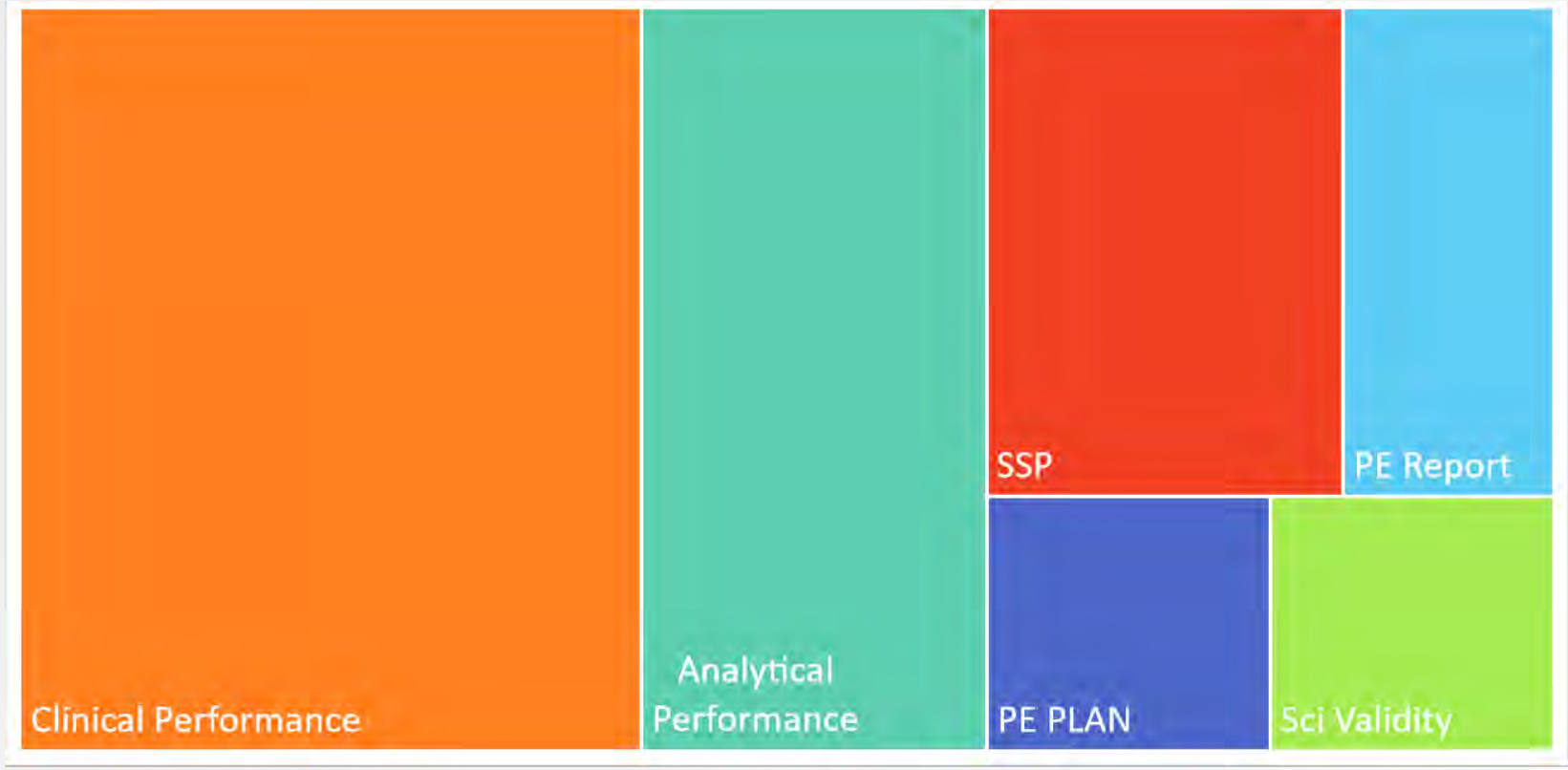
The sum of all Performance Evaluation Documentation



Analysis of Questions on PE / Clinical Evidence

Majority of questions centre around information provided for Clinical Performance (>40%)

For information on PE plans, Scientific Validity, Analytical Performance and PE Reports please revisit previous BSI webinars https://www.bsigroup.com/en-GB/medical-devices/resources/webinars/IVDR-webinars/



Definitions

IVDR Article 2 (41)

'Clinical performance' means the ability of a device to yield results that are correlated with a particular clinical condition or a physiological or pathological process or state in accordance with the target population and intended user.

The clinical performance should demonstrate that the IVD:

- Can achieve clinically relevant outputs through predictable and reliable use by the intended user(s).
- Has been tested for the intended use(s), target population(s), use condition(s), operating and use environment(s) and with all the intended user group(s).

Indicators of clinical performance vary and depend strongly on the intended purpose and performance claims.

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Clinical performance characteristics

Clinical Performance can be characterised by the demonstration and evaluation of applicable aspects to the device under review (Annex I 9.1b):

- Diagnostic sensitivity,
- Diagnostic specificity,
- Positive predictive value,
- Negative predictive value
- Positive likelihood ratio,
- Negative likelihood ratio,
- Expected values (normal and affected populations)

Not all the above maybe applicable, it depends on the device.

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IVDR Mandated Performance Evaluation Documents – Annex XIII

Initial Documentation

Performance Evaluation Plan

Scientific Validity Report

Analytical Performance Report

Clinical Performance Report

- Clinical Performance Study Plan(s)
- Clinical Performance Study Report(s)

Performance Evaluation Report (inc. literature search protocols and reports)

Living document!

Post-Market Performance Follow Up Plan

Additional Documentation Post-certification

Post-Market Performance Follow Up Report(s)

Associated Documents

PMS Plan

Risk Management documentation

SSP

PSUR or PMS Report

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IVDR Mandated Performance Evaluation Documents

Initial Documentation

Performance Evaluation Plan

Scientific Validity Report

Analytical Performance Report

Clinical Performance Report

- Clinical Performance Study Plan(s)
- Clinical Performance Study Report(s)

Performance Evaluation Report (inc. literature search protocols and reports)

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Associated Documents

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Risk Management documentation

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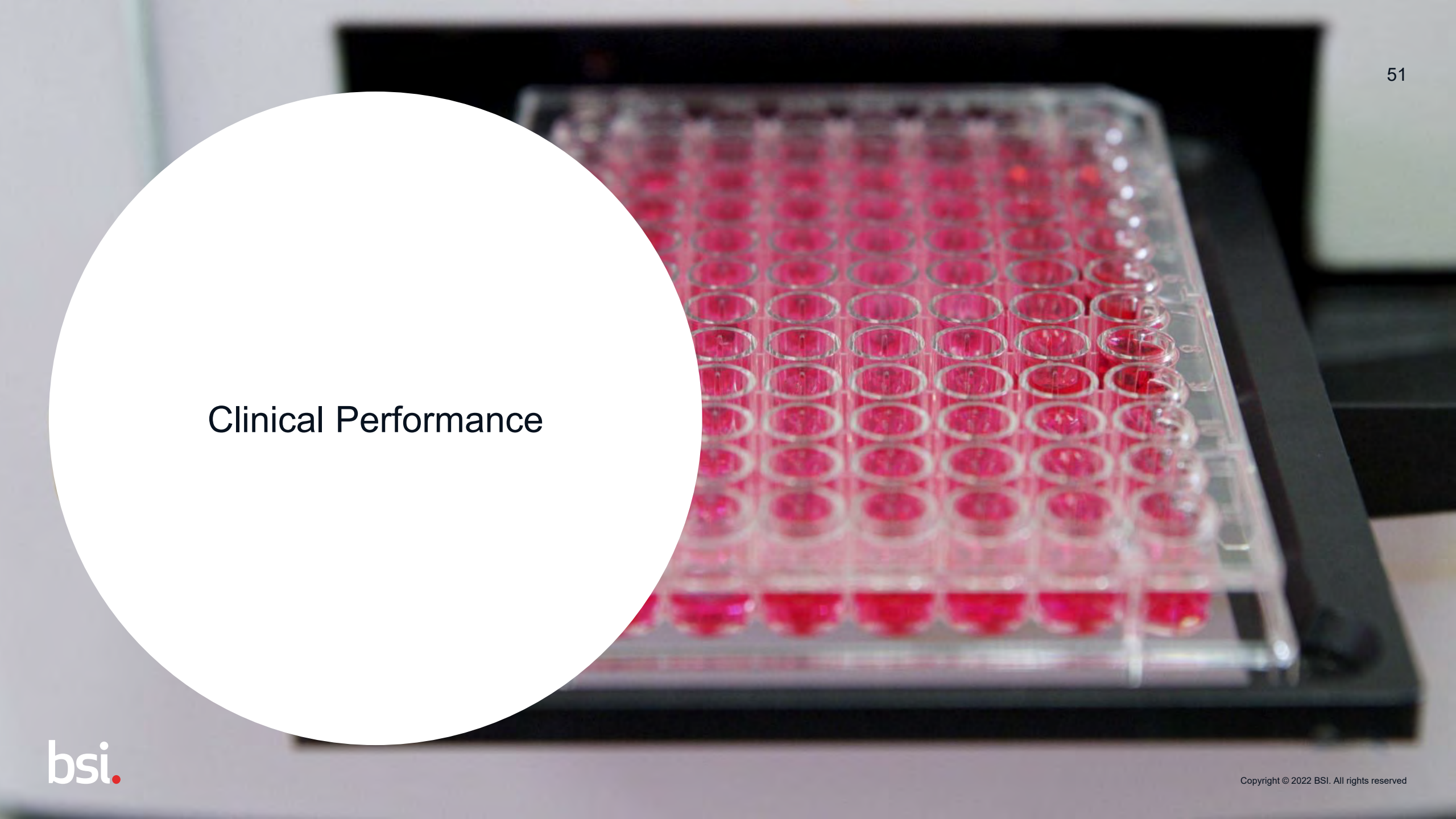
Clinical Performance



Clinical Performance

Intended Purpose

Is it clear?

Does it represent clinical state-of-the-art in the EU for the analyte and clinical condition?

Before you start

Ensure your strategy for Clinical Performance matches your Intended Purpose

Revisit throughout the product development process – *is the strategy still appropriate?*

Clinical Performance Requirements – Annex XIII 1.2.3

Demonstration of the clinical performance of a device **shall** be based on one or a combination of the following sources

Clinical performance studies 1

Scientific peer-reviewed literature 2

Published experience gained by routine diagnostic testing 3

and other sources of clinical data 4

*"Clinical performance studies **shall** be performed unless due justification is provided for relying on other sources of clinical performance data."*

A combination of methods may be necessary

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1 Clinical Performance Studies

Annex XIII Part 2

2.1 Purpose of clinical performance studies

2.2 Ethical considerations

2.3 Methods

2.3.1 Study design

2.3.2 Clinical Performance Study Plan

2.3.3 Clinical Performance Study Report

3 Other performance studies

*** ISO 20916:2019 - In vitro diagnostic medical devices. Clinical performance studies using specimens from human subjects. Good study practice**

New to market devices should use the Clinical Performance Study route to establishing Clinical Performance

Clinical Performance Studies – points to consider

Patient population

Should cover the entire intended use population.

Sample types

Should cover all types indicated in the IFU.

Are frozen archived samples appropriate if IFU requires fresh?

Rare samples / markers – what is your strategy?

Comparator device

Is it a state-of-the-art device in Europe? Justify!

Composite reference standards for novel markers – comprehensively justify.

Plan for resolving discordant results? Which device represents truth? Why?

Non-EU study location(s)

Is the patient demographic appropriate for the EU population? Justify:

Genetic / physiological marker prevalence

Infectious agent strain / serotype prevalence

Can you really justify internal clinical performance studies?

Study users

Professional users – are they representative of European professional users and lab conditions?

Near-patient tests – consider variations in healthcare training across Europe.

Self-tests – do they match the EU intended purpose demographic? Age, educational background, technology use?

You may need more than one Clinical Performance Study to prove the full intended purpose

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Clinical Performance Studies – legacy IVDD devices

"Clinical Performance Studies" **do not meet the requirements of Annex XIII 2.3**

- **Studies were performed to meet requirements of IVDD not IVDR**
- **These are 'other sources of clinical data'**

✓ **Justification required for why clinical performance studies were not done, new strategy required in PE Plan to demonstrate Clinical Performance**

OR

✓ **Gap analysis to show why missing elements of Annex XIII 2.3 were appropriate for the study purpose**

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Clinical Performance Study documentation - Annex XIII Part 2

2.3.2 Clinical Performance Study Plan(s)

"*The CPSP shall define the rationale, objectives, design and proposed analysis, methodology, monitoring, conduct and record-keeping*…"

"*It shall contain in particular the following information:* …"

Followed by a long list of requirements.

Justify non-applicable requirements.

2.3.3 Clinical Performance Study Report(s)

"*The results and conclusions shall be transparent, free of bias and clinically relevant*."

"*The report shall contain sufficient information to enable it to be understood by an independent party without reference to other documents*."

"*The report shall also include as appropriate any protocol amendments or deviations, and data exclusions with the appropriate rationale*."

Signed by a medical practitioner or any other authorised person responsible.

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2 Scientific peer-reviewed literature

The majority of legacy devices reviewed by BSI use this as the main pillar of clinical performance

Usually supported by IVDD performance data and/or PMS data as a source of "other sources of clinical data" data

Performance Evaluation Report requirements (Annex XIII 1.3.2) link to this.

This report **shall** include:

the justification for the approach taken to gather the clinical evidence;

the literature search methodology and the literature search protocol and literature search report of a literature review; …

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Scientific peer-reviewed literature – typical gaps

Publications reviewed should include:

- ➢ The device under application used per intended purpose
- ➢ All sample types or clinical conditions claimed in the IFU
- ➢ Source should be peer-reviewed e.g. conference poster presentations are not appropriate

Acceptable publications:

- ✓ Any full publication in a peer reviewed journal
- ✓ Any published document from major medical/clinical organisations e.g. WHO, EMA, clinical reference lab.

Consider the age of the information. Is it still state-of-the-art?

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Literature Review - consider

Annex VII states that the NB shall review the methodology for Literature searching:

The literature review must be ‘systematic’

GHTF guidance available: GHTF/SG5/N7:2012

IVDR literature searching guidance not available, small amount of information available in MDCG 2022-2

Applies to Clinical Performance literature review and Scientific Validity Literature review

3 Published experience gained by routine diagnostic testing

"Published":

Made available to the public and with an identifiable source

"Routine diagnostic testing":

The device being used according to its *routine intended purpose* on the EU population

➢Examples

✓**Data from proficiency testing / ring trials or external quality assurance (EQA) schemes**

✓**Poster presentation data IF documenting *routine diagnostic testing***

✓***Others…?***

Justify '*published*' if it is not obvious

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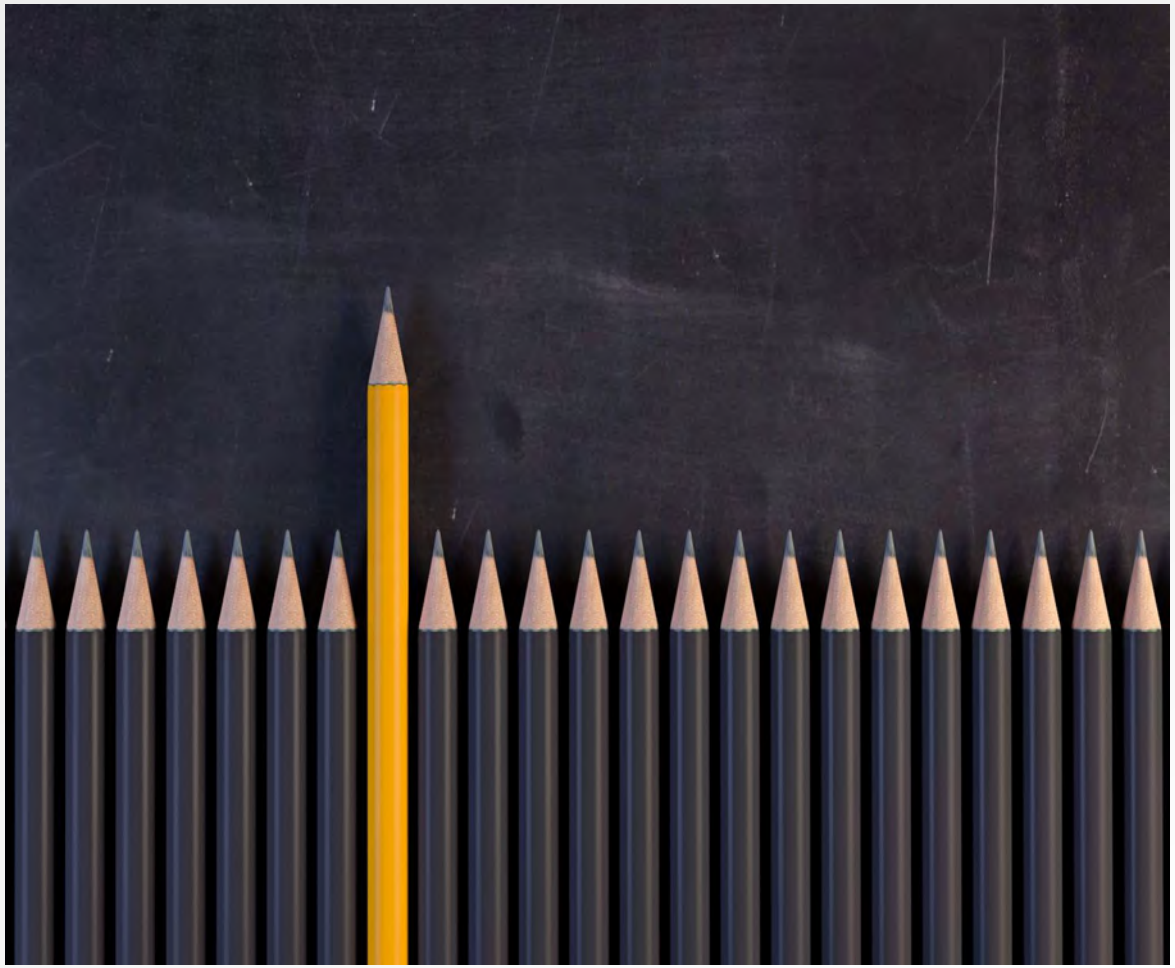
What can EQA and ring trial data demonstrate for IVDR?

- ✓ How the device under review is performing across multiple labs
- ✓ How the device is performing versus similar devices
- ✓ Data generated on appropriate patient like sample types to the intended use of device
- ✓ Show device performance across appropriate ranges/clinical decision points of the analyte

Needs to be of appropriate depth, quality and quantity to demonstrate Clinical Performance



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Limitations of using EQA data to support Clinical Performance

Relevance

The primary purpose of EQA is not to support the Clinical Performance claims of an IVD

Ensure EQA data provided is relevant

Sample types

Sample types may be contrived or synthetic

EQA schemes include ‘educational’ samples as well as core samples

Source of testing

EQA data in a manufacturers own lab is not as strong as evidence from clinical laboratories compared across similar devices

Ring trials have similar limitations

4 Other sources of clinical data…

IVDD or clinical data from other jurisdictions

Must be applicable to the European population

Must have a plan and report as per Annex XIII Part 2 requirements

Not acceptable to use alone without one of the three pillars of evidence *unless justification provided*

BSI accepted justifications (so far)

Companion Diagnostic – device was used in the pivotal clinical trial for the medicinal product and therefore medicinal legislation is judged as conforming to the general principles of IVDR

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A note on Equivalence

Demonstrating clinical evidence via equivalent devices is a strategy for medical devices that is typically justified to avoid invasive clinical procedures.

Equivalence *cannot* be claimed for IVDs *unless* the critical elements of the devices can be proven to be ***identical***

- Primers / probe sequences
- Antibody clones
- Enzymes

(including reaction concentrations and conditions).

Clinical Performance Report

Annex XIII 1.2.3

"*Clinical performance shall be demonstrated and documented in the clinical performance report*"

Clinical Performance Report

Write up and summarise all of your clinical performance activity in the CPR

If you have used more than one of the methods, bring them all together and summarise.

Performance Evaluation Report (Annex XIII 1.3.2)

"*This report shall include the scientific validity report, the analytical performance report, the **clinical performance report** and an assessment of those reports allowing demonstration of the clinical evidence*."

"*Shall include … the justification for the approach taken to gather the clinical evidence*;"

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How much is enough clinical performance data?

!!! This is impossible to quantify !!!

Huge variety of IVDs, Intended Purposes, patient populations and risks

There are multiple options on how to demonstrate Clinical Performance

The Notified Body will assess all sources of Clinical Performance data claimed and collectively determine if the quality and quantity supports the claims

- **Clinical Performance Study Sample Numbers**

How many samples are enough?

Million dollar question! Inappropriate for NB to say as we cannot consult.

- **Peer-reviewed scientific literature:**

How many publications are enough?

The number of publications is not important. Review content of the publications, the quality and quantity of data e.g. how many samples used and assessment conducted. What does the data show? Is it state-of-the-art?

- **EQA data:**

How many samples? How many cycles per year? How many years data provided? How many labs use your device?

Many Mfrs provide one year of data…… this isn't generally enough on its own.

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Post Market Performance Follow-Up, Annex XIII Part B

Post Market Performance Follow-Up can be used to mitigate outstanding risks if:

- There are outstanding performance and safety risks after completing appropriate Performance Evaluation

AND

- The existing data supports a benefit : risk ratio that justifies placing the product on the market

E.g. rare sample types or markers cannot be sourced during clinical performance studies

E.g. after placing on the market, new and emerging risks are identified via PMS

Justify why the device is still safe to place on the market, prepare a robust PMPF plan and *follow it through*

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Learning Points…

- **Clinical Performance** may be from multiple sources Must be from at least one of 3 elements listed in Annex XIII
- Justification for ***not*** performing Clinical Performance Studies should be clear and valid
- '**Clinical Performance Studies**' must meet requirements of Annex XIII 2.3
- Link to **Post-Market Performance Follow-up** - Further studies may be needed if there are residual risks not addressed by the clinical evidence provided or if state-of-the-art changes on market
- The Notified Body will assess all sources of Clinical Performance data claimed and collectively determine if the **quality and quantity supports the device claims**

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Guidance

MDCG 2022-2 - Guidance on general principles of clinical evidence for In Vitro Diagnostic medical devices (IVDs)

MDCG 2022-9 - Summary of safety and performance template

ISO 20916:2019 - In vitro diagnostic medical devices. Clinical performance studies using specimens from human subjects. Good study practice

MDCG 2022-10 - Q&A on the interface between Regulation (EU) 536/2014 on clinical trials for medicinal products for human use (CTR) and Regulation (EU) 2017/746

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High Risk IVD's update: current status of CDx and Class D devices

Alex Laan
Head IVD Notified Body– IVD devices, BSI

25 April 2023

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High Risk IVD's update: current status of CDx and Class D devices

1. High Risk IVD's conformity assessment per IVDR
   - General certification process for CDx
   - General certification process for Class D IVD's
2. Current notified body experience with certifying high risk IVD's
   - IVDD versus IVDR requirements
   - Experience of existing applications
   - Status of EMA consultations
   - Status of EU Reference Labs
3. Questions and Answers

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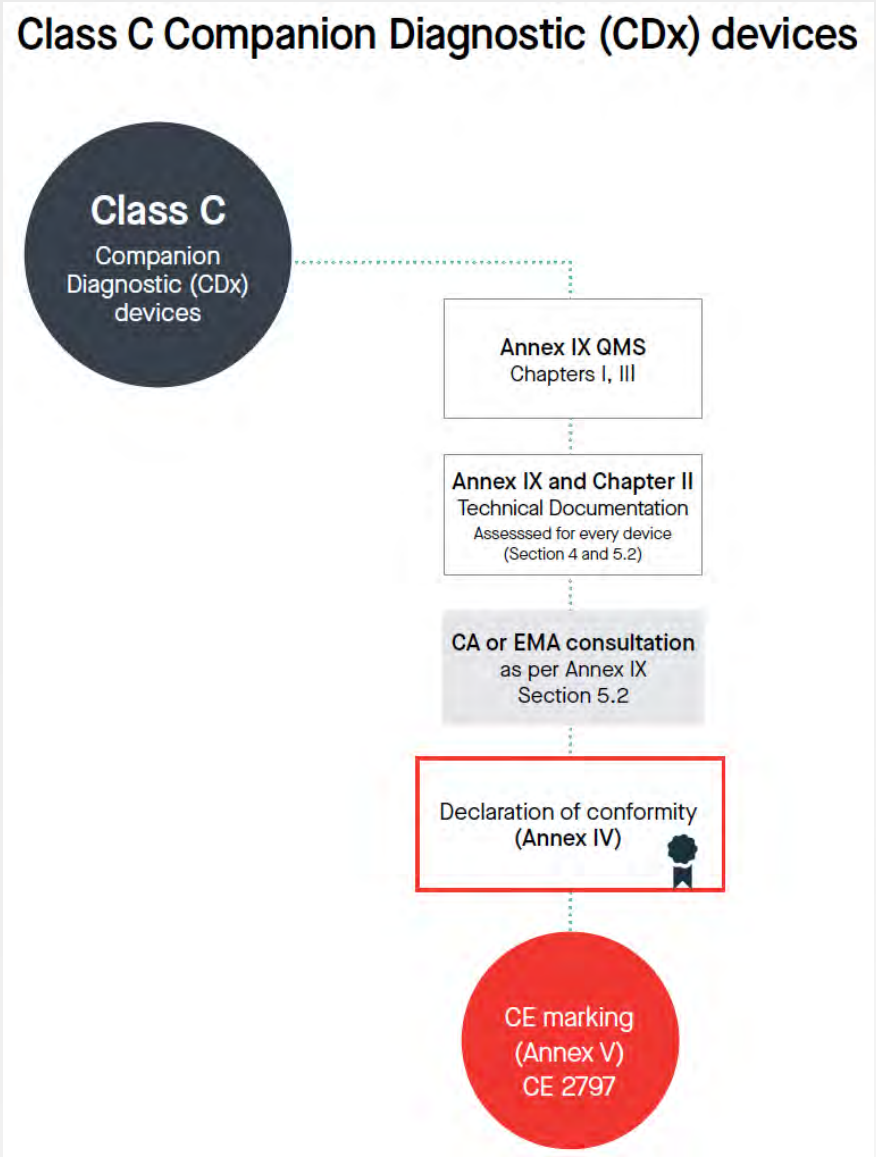
High Risk IVD's conformity assessment per IVDR – Companion Diagnostics



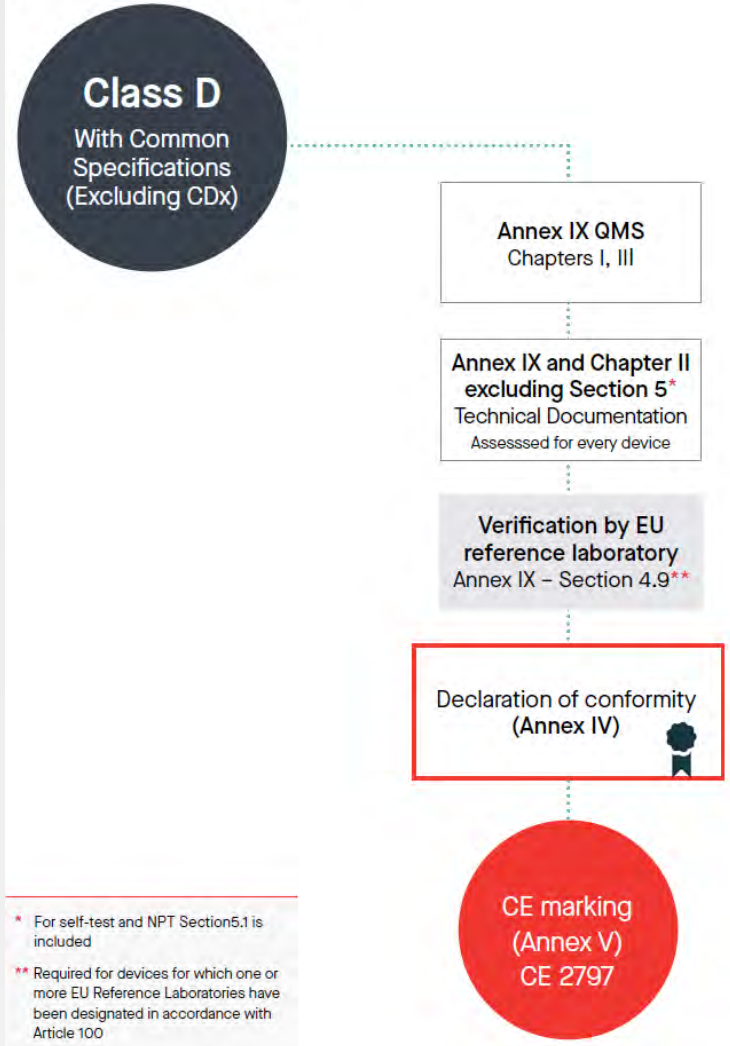
Applicable audits, assessments and requirements

Class C Companion Diagnostic (CDx) devices

Class C Companion Diagnostic (CDx) devices	Initial Conformity Assessment	Surveillance				
		Y1	Y2	Y3	Y4	Y5
QMS Audits	Yes	Yes	Yes	Recert**	Yes	Yes
Microbiology Audits	Yes*	N/A	N/A	Yes*	N/A	N/A
Technical Documentation Assessment	Review for every device	N/A	N/A	N/A	N/A	Recert
Competent Authority or EMA consultation (Annex IX, Section 5.2)	Yes	Modifications to the devices may need supplementary consultations (determined on a case-by-case basis taking into account the nature of the changes proposed)				
Experts consultations (article 48(6))	N/A	N/A	N/A	N/A	N/A	N/A
Verification by EU reference laboratory (Annex IX, section 4.9)	N/A	N/A	N/A	N/A	N/A	N/A
Summary of Safety and Performance (Article 29)	Yes	Updated as soon as possible, where necessary				
Performance Evaluation Report updates (Annex XIII - Part A, Section 1.3.2 and Article 56)		Updated at least annually. Notified Body to review at the time of PSUR reviews or substantial change reviews				
Post Market Performance Follow-up (PMPF) updates Evaluation Report (Article 56 and Annex XIII, Part B)		Updated as per manufacturer's PMS, PMPF plans. Notified Body to review at the time of PSUR reviews or substantial change reviews				
Post Market Surveillance (PMS) Report (Article 80)		Post-market surveillance will be captured in the Periodic Safety Update Report				
Periodic Safety Update Report (PSUR) (Article 81)		PSUR update required at least annually. The PSUR should be available to the Notified Body upon request				
Unannounced Audits		At least once every 5 years				

High Risk IVD's conformity assessment per IVDR – Class D IVD's

Class D with Common Specifications (Excluding CDx)



* For self-test and NPT Section5.1 is included

** Required for devices for which one or more EU Reference Laboratories have been designated in accordance with Article 100

Applicable audits, assessments and requirements

Class D with Common Specifications (Excluding CDx)

Class D with Common Specification (Excluding CDx)	Initial Conformity Assessment	Surveillance				
		Y1	Y2	Y3	Y4	Y5
QMS Audits	Yes	Yes	Yes	Recert*	Yes	Yes
Microbiology Audits	Yes*	N/A	N/A	Yes*	N/A	N/A
Technical Documentation Assessment	Review for every device	N/A	N/A	N/A	N/A	Recert
Competent Authority or EMA consultation (Annex IX, Section 5.2)	N/A	N/A	N/A	N/A	N/A	N/A
Experts consultations (article 48(6))	N/A	N/A	N/A	N/A	N/A	N/A
Verification by EU reference laboratory (Annex IX, section 4.9)	Yes	Modifications to the devices may need supplementary verifications (determined on a case-by-case basis taking into account the nature of the changes proposed)				
Summary of Safety and Performance (Article 29)	Yes	Updated as soon as possible, where necessary				
Performance Evaluation Report updates (Annex XIII - Part A, Section 1.3.2 and Article 56)		Updated at least annually. Notified Body to review at the time of PSUR reviews or substantial change reviews				
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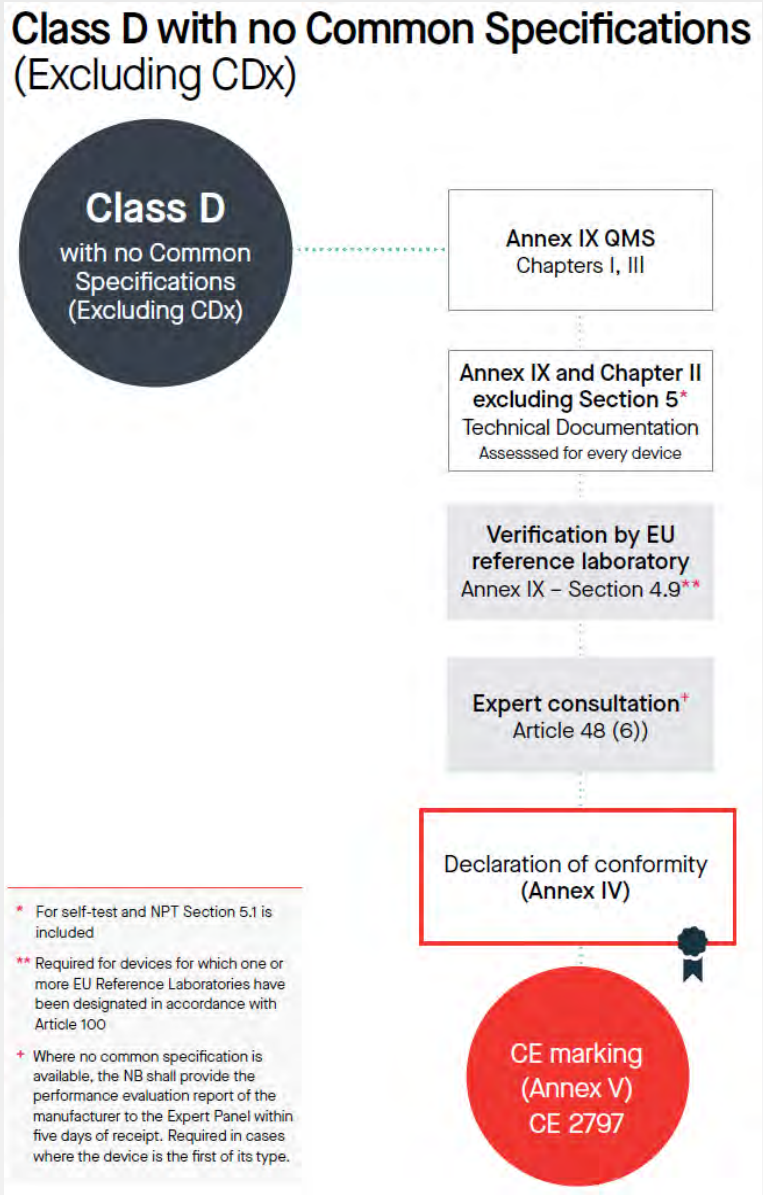
Post Market Surveillance (PMS) Report (Article 80)		Post-market surveillance will be captured in the Periodic Safety Update Report				
Periodic Safety Update Report (PSUR) (Article 81)		PSUR update required at least annually. Submitted to the Notified Body via EUDAMED for Notified Body review				
Unannounced Audits		At least once every 5 years				

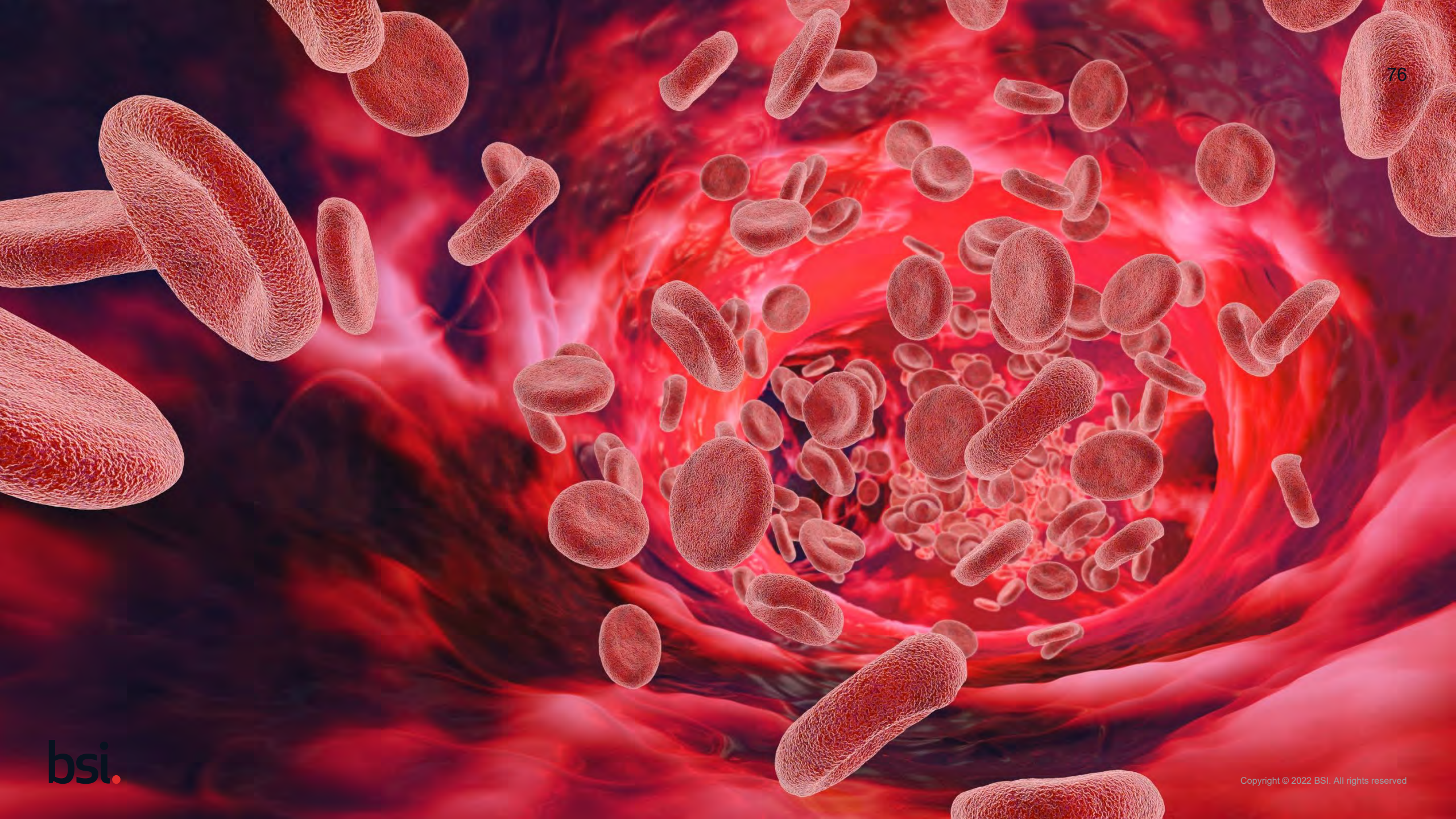
High Risk IVD's conformity assessment per IVDR – Class D IVD's



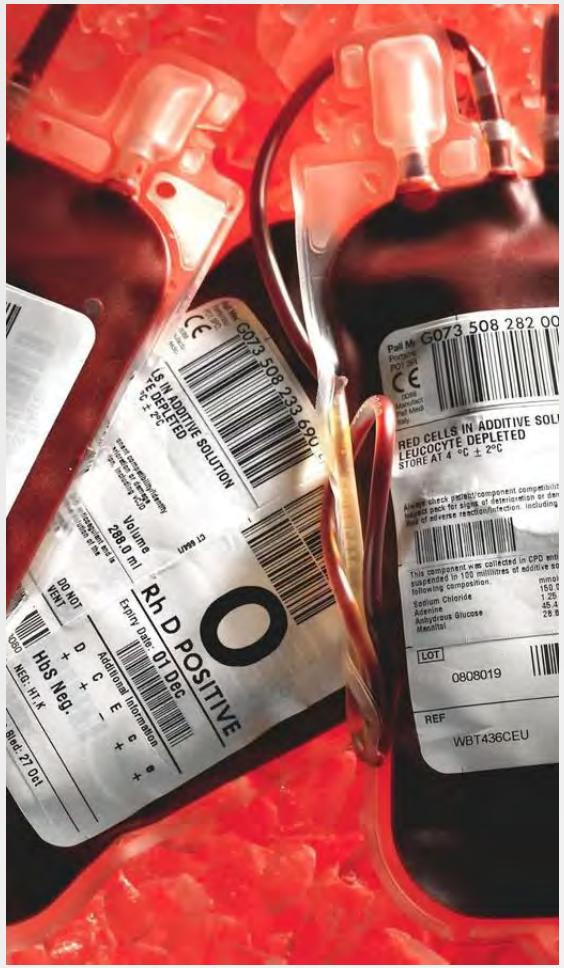
Applicable audits, assessments and requirements

Class D with no Common Specifications (Excluding CDx)

Class D with no Common Specifications (Excluding CDx)	Initial Conformity Assessment	Surveillance				
		Y1	Y2	Y3	Y4	Y5
QMS Audits	Yes	Yes	Yes	Recert**	Yes	Yes
Microbiology Audits	Yes*	N/A	N/A	Yes*	N/A	N/A
Technical Documentation Assessment	Review for every device	N/A	N/A	N/A	N/A	Recert
Competent Authority or EMA consultation (Annex IX, Section 5.2)	N/A	N/A	N/A	N/A	N/A	N/A
Experts consultations (article 48(6))	Yes if the device is the first of its type	N/A	N/A	N/A	N/A	N/A
Verification by EU reference laboratory (Annex IX, section 4.9)	N/A	Modifications to the devices may need supplementary verifications (determined on a case-by-case basis taking into account the nature of the changes proposed)				
Summary of Safety and Performance (Article 29)	Yes	Updated as soon as possible, where necessary				
Performance Evaluation Report updates (Annex XIII - Part A, Section 1.3.2 and Article 56)		Updated at least annually. Notified Body to review at the time of PSUR reviews or substantial change reviews				
Post Market Performance Follow-up (PMPF) updates Evaluation Report (Article 56 and Annex XIII, Part B)		Updated as per manufacturer's PMS, PMPF plans. Notified Body to review at the time of PSUR reviews or substantial change reviews				
Post Market Surveillance (PMS) Report (Article 80)		Post-market surveillance will be captured in the Periodic Safety Update Report				
Periodic Safety Update Report (PSUR) (Article 81)		PSUR update required at least annually. Submitted to the Notified Body via EUDAMED for Notified Body review				
Unannounced Audits		At least once every 5 years				



Class D devices – current status



Class D devices have a **HIGH** public health risk and/or a **HIGH** personal risk

IVDD written after the contaminated / infected blood scandal of the 1970s and 1980s.

- Devices that detect and screen for HIV-1 and -2, Hepatitis B, C and D and HTLV I and II
- Many IVDD NBs use Paul Ehrlich Institute (PEI) to test / release IVDD List A devices

IVDR Rule 1 expands the highest risk IVDD devices to include:

- All transmissible agents in blood components, cells, tissues, organs
- Transmissible agents that cause a life-threatening disease with a high or suspected high risk of propagation
- Devices for determining infectious load of a life-threatening disease where monitoring is critical

IVDR Rule 2 includes

- The same Blood Grouping markers as IVDD Annex II List A plus Duffy and Kidd system devices classified as Annex II List B

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Class D devices – current status

IVDR Article 100 European Reference Laboratories (EURL)

- 2(a) verify performance claimed and compliance of Class D devices to applicable CS
- 2(b) carry out appropriate tests on samples of manufactured class D batches

There are no EURLs designated today

MDCG 2021-4 - *Application of transitional provisions for Class D*

- Notified Bodies can proceed without designated EURL i.e. Article 100 requirements should be dealt with via internal NB processes

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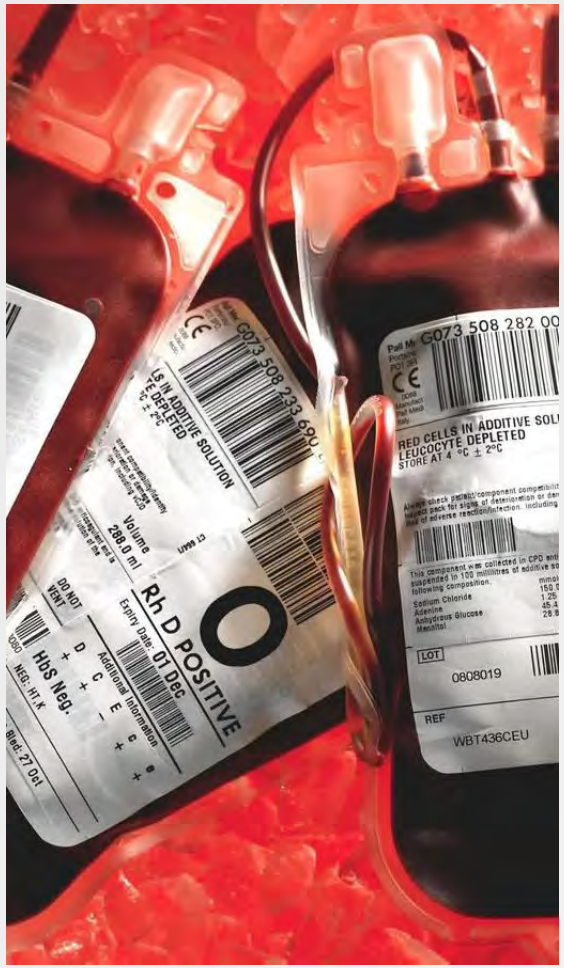
Class D devices – BSI current status



- IVDR conformity assessment to proceed
- Manufacturers batch release controls will be scrutinised during initial conformity assessment to ensure maintenance of current batch-to-batch reproducibility
- Conformity assessment will result in agreement of batch release risk mitigations between NB and manufacturer
- If Common Specification applies, device should meet requirements or have appropriate benefit : risk justification for gaps
- BSI also pursuing alternative independent testing options with the Notified Body Class D working group in line with TEAM-NB position paper

https://www.team-nb.org/class-d-measures-in-the-absence-of-eu-reference-laboratories/

EU Reference Laboratories Designation – expected Q3 2023 but could take longer…

See Commission Rolling Plan:

https://health.ec.europa.eu/system/files/2022-12/md_rolling-plan_en.pdf

- Some exclusions apply due to patient safety concerns

Class D devices and PECP oversight

Class D – BSI position

IVDD self-declared devices - progress when our technical experts are able to get on-site to witness testing. Batch records and PMS data will be assessed during initial assessment.

Blood grouping – progress unless novel. Batch records and PMS data will be assessed.

Former Infectious disease List A devices that – we will start review but cannot issue certificate without EURL or other solution in place.

New to market Class D devices – we will start the review but cannot issue certificate without EURL or other solution.

EURL alternative solutions – NB Class D working group

Alternative subcontractor test lab.

EQA providers / use of blinded panels.

Witness testing during audits.

Additional oversight on post market and vigilance data as part of IVDR conformity assessment.

PECP oversight

Time sensitive.

Manufacturers should incorporate all PE documentation and IFU into their PE Report.

Manufacturers should review existing PECP views and CS to identify themes that could apply to their device.

PECP comments about analytes with low EU prevalence require strong justification from the manufacturer about PE strategy.

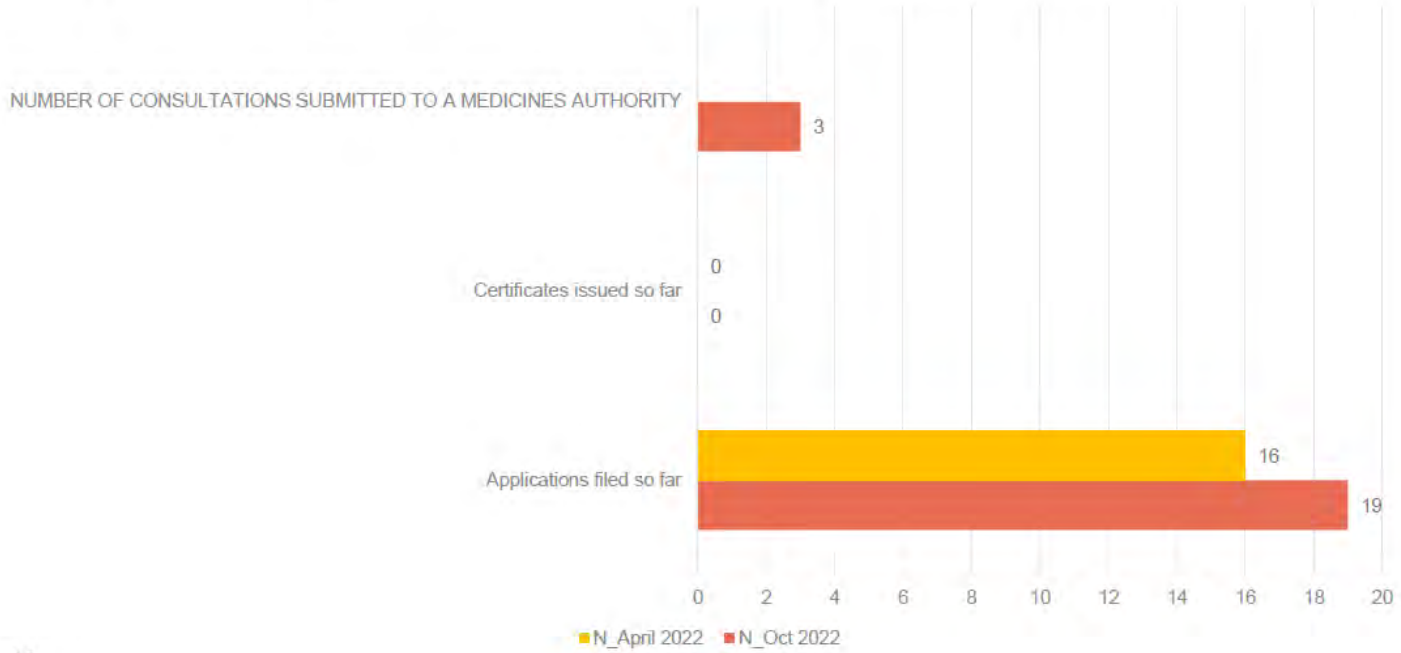
Companion Diagnostics – current status

IVD

Survey on certifications and applications

IVDR Applications and Certificates –
Companion diagnostic devices requiring consultation

IVDR Data (4/5)



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European Commission

Companion Diagnostics – current status

Conformity assessment of Companion Diagnostics is progressing, current experiences are as follows:

- Quality and extend of technical documentation of CDx is variable across all applications, especially between SME's and larger IVD manufacturers.
- Level of detail in the IFU and (draft) SSP is not always to the same degree as the EMA would expect it to be.
- Classification of CDx (or substantiation of this) sometimes leads to questions.
- EMA delivers its opinion within 60 days, the submission logistics can be challenging keeping in mind the pre-defined clock-stops.
- Different strategies apply for Co-developed CDx, Follow-On CDx and Legacy CDx.
- EMA shall deliver a scientific opinion on the *suitability of the device in relation to the medicinal product concerned;* this is something different to the role of the Notified Body; conformity assessment to IVDR.

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Companion Diagnostics – top tips for technical documentation

Scientific validity

EMA status of the medicinal product should be referenced. Device is not valid as an IVDR CDx without a corresponding drug.

If EMA are still reviewing the drug, be transparent in technical documentation.

FDA status of the drug / device has no relevance to IVDR documentation.

Clinical Performance

Co-developed devices

Reference European registered pivotal clinical trials where device was used.

If the device has changed since the trials, clearly document bridging studies.

BSI is accepting pivotal clinical trial study plans as Annex XIII compliant Clinical Performance Study Plans.

Me-too / Follow-on CDx

Concordance studies should be with the pivotal clinical trial device and use the clinical trial samples.

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Current notified body experience with certifying high risk IVD's

In general, it is a challenging process to certify companion diagnostics and Class D IVD's, due to the following reasons:

- Consultation process of CDx at EMA is still developing; still a steep learning curve.
- Quality and extent of technical documentation of CDx is variable across the board, but this also depends on the scenarios that the manufacturer applies
- Class D certification applications are accepted but for the majority of devices, especially intended for blood safety testing, batch verification evidence is required.
- Class D certification is progressing without the use of EURLs, with the use of alternative measures as previously described. But this process requires additional resources from both QMS auditors and Technical Specialists.
- Common Specifications for Class D's have been released in 2022, but these need to be incorporated by IVD manufacturers when applying with a Notified Body.

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IVDR CDx and Class D's – Final Comments…

- **Challenges for Class D and Companion Diagnostic devices remain for the moment, but process is made among Notified Bodies in certifying these devices**
- **Learning curve with Notified Bodies as well as EMA for CDx**
- **Progress is being made for designation of EURL's in the EU, still a wait and see approach**
- **Capacity with BSI for these devices is keeping to expand, which will help to meet the deadlines**

As with everything, dealing with changes is difficult…but try to "embrace the grey" for now. Do not get stuck in the sand ↓

Guidance

MDCG Endorsed Documents:

https://health.ec.europa.eu/medical-devices-sector/new-regulations/guidance-mdcg-endorsed-documents-and-other-guidance_en

BSI IVD website:

https://www.bsigroup.com/en-GB/medical-devices/our-services/IVDR-Revision/

- Webinars
- Whitepapers
- Training Courses

Q & A Session

IVDR resources to support you

BSI IVD website

www.bsigroup.com/IVDR

- Guides
- Webinars
- Whitepapers
- Training courses

Contact us

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