Best Tools & Tricks for Meeting IVDR Requirements to Obtain CE Marking

8 October 2020 | Free Live Webinar

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Topics

I. Understanding your existing gaps
II. Change impact
III. Planning the pathway forward
IV. Evidence evaluation
V. Planning ongoing compliance

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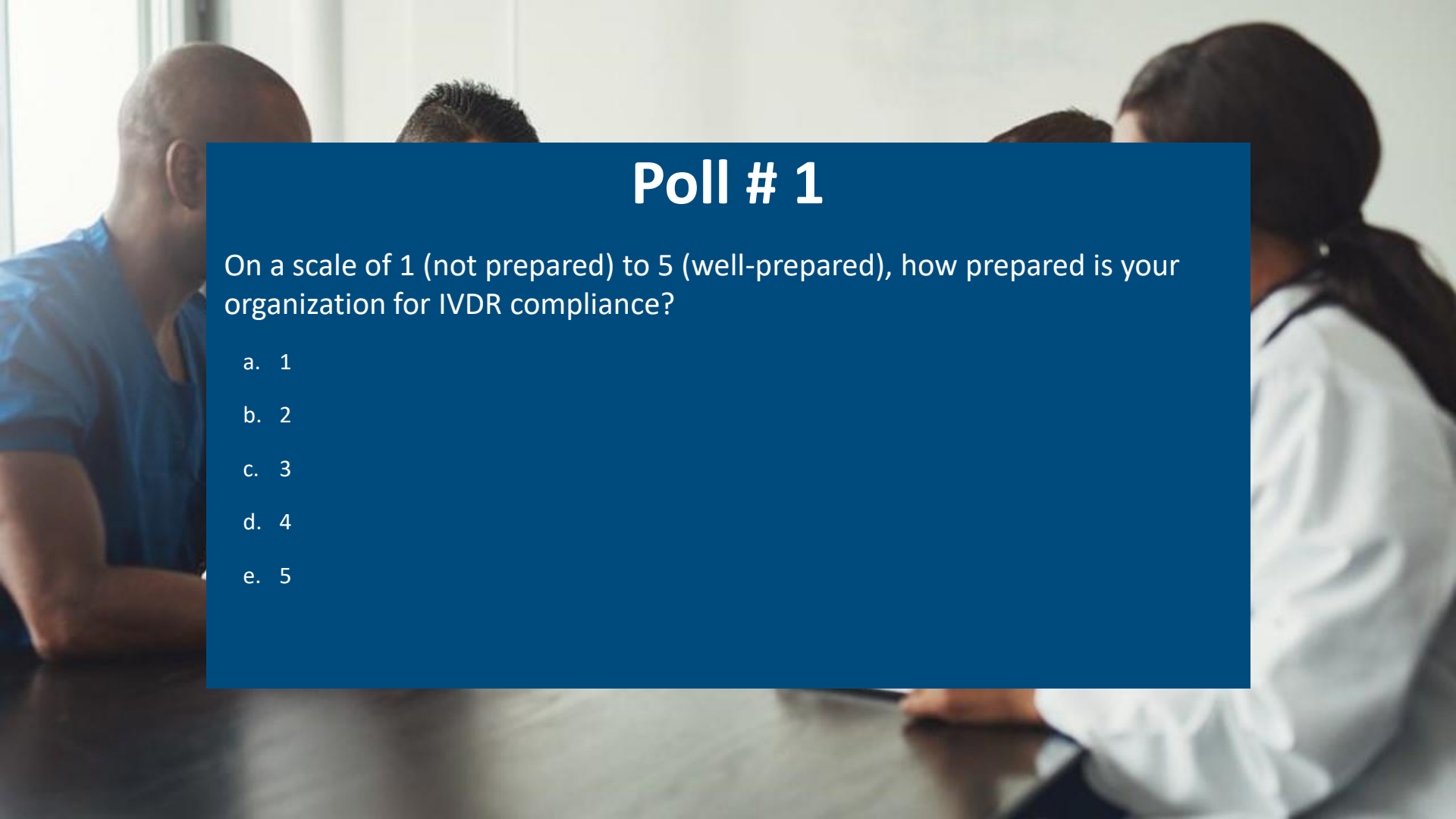


Poll # 1

On a scale of 1 (not prepared) to 5 (well-prepared), how prepared is your organization for IVDR compliance?

a. 1

b. 2

c. 3

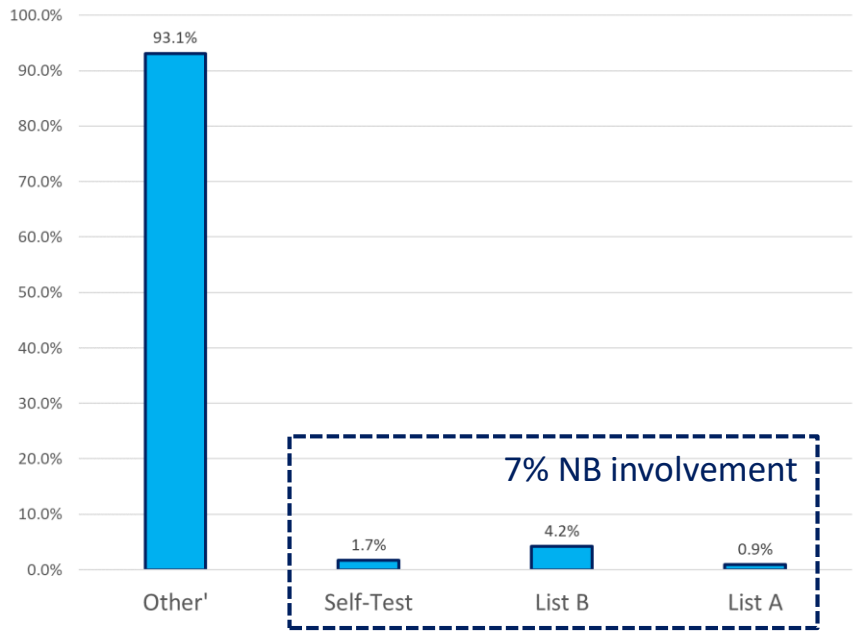
d. 4

e. 5

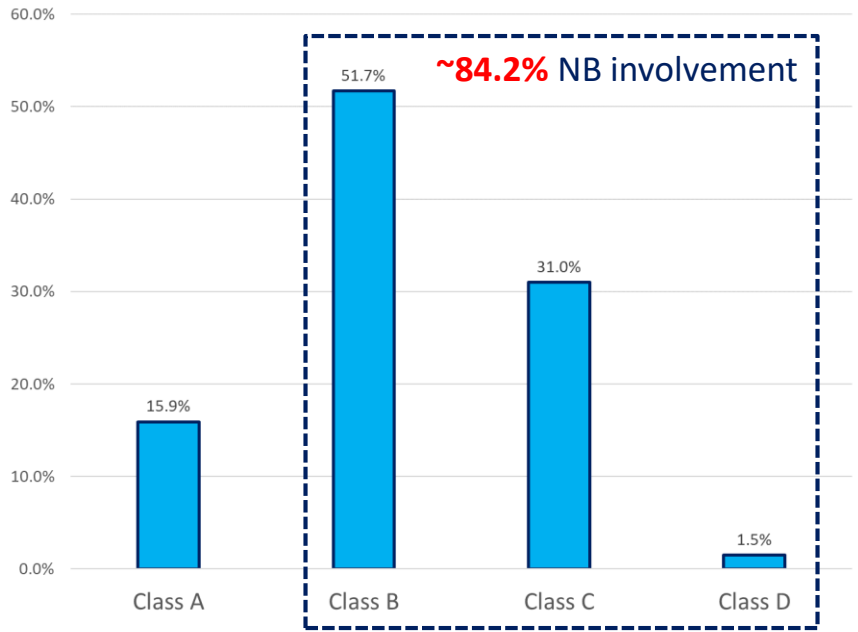
Understanding your existing gaps

Shift in Notified Body Involvement

IVDD 98/79/EC



IVDR 2017/746



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Source: A. van Drongelen et al."The impact of the new European IVD-classification rules on the notified body involvement; a study on the IVDs registered in the Netherlands". RIVM Letter report 2018-0082. Commissioned by The Dutch Health and Youth Care Inspectorate

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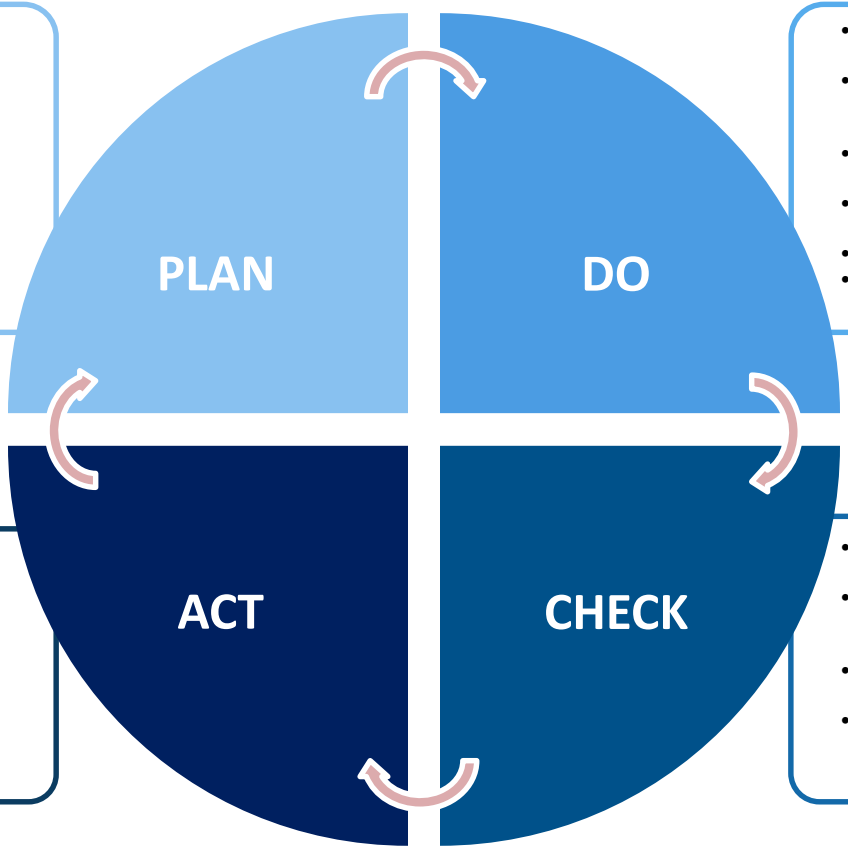
Issues with Self-Certified IVDs

- Lack of or poor planning:
  - Design & Development
  - Risk Management
  - Performance Evaluation
  - PMS
- Lack of or poor understanding of requirements:
  - Application of incorrect or obsolete HS
  - Incorrect determination of ER applicability



- Insufficient analytical or clinical performance evaluation
- Poor or missing rationales or justifications (e.g. SoA vs. statistical basis of sample sizes in testing)
- Insufficient consideration of assay workflow (sampling -> test result)
- Not following QMS processes (e.g. document control)
- Critically deficient RM documentation
- Lack of usability considerations

- Not performing post-market activities as planned (e.g. not checking whether virus mutations could impact device performance)
- Not making design changes in according with planned arrangements

- Fundamental lack of understanding of PMS or not performing PMS
- Not checking for legacy text in 'copied and pasted' text from other IVDs, particularly in labeling
- Not checking for non-translated text or information
- Missing or deficient benefit-risk analysis

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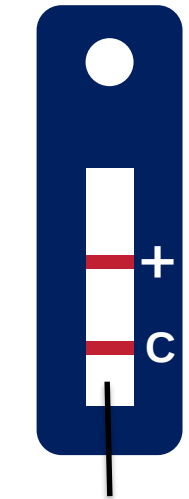
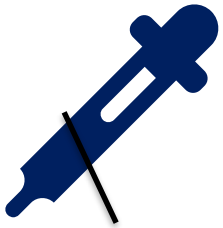
Example of Issues with Self-Certified IVDs

ER B3.4

Devices must be designed and manufactured in such a way as to reduce as far as possible the risks of fire or explosion during normal use and in single fault condition. Particular attention must be paid to devices whose intended use includes exposure to or use in association with flammable substances or substances which could cause combustion.



Nitrocellulose

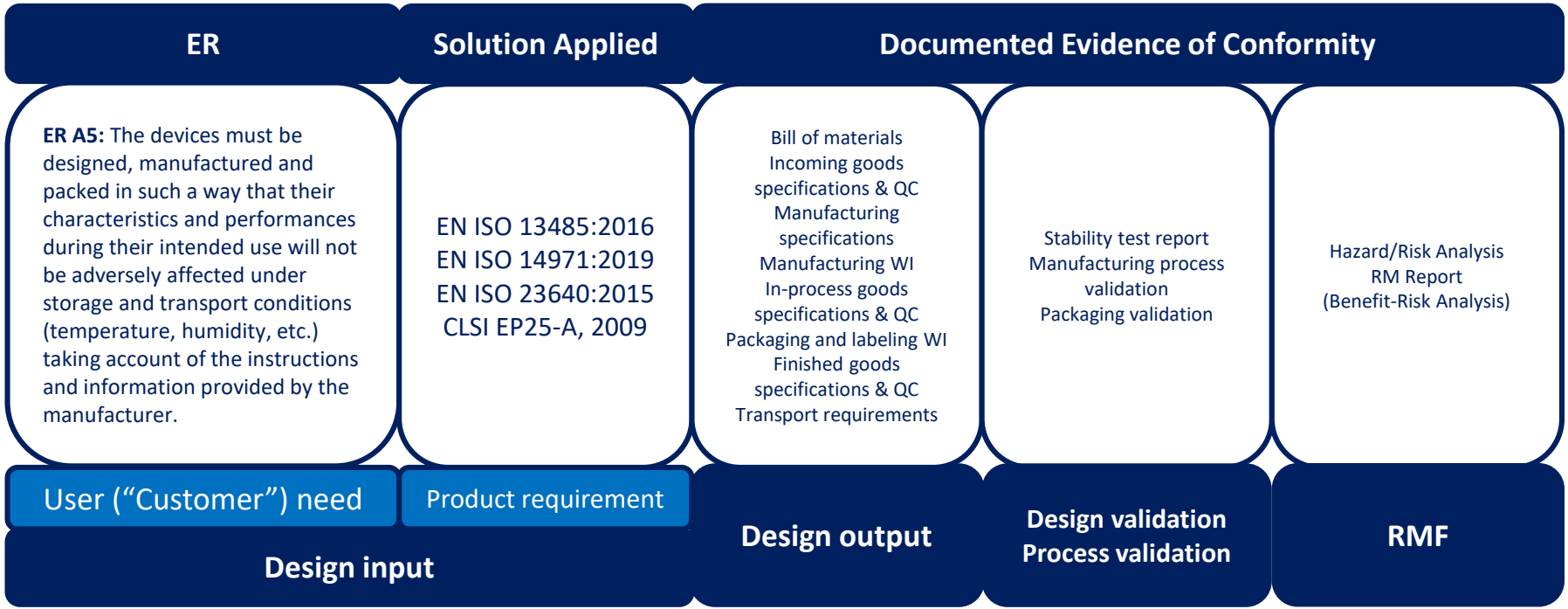


Sodium Azide

EN ISO 14971

- Safety by design
- Protective measures
- Information for safety

The ER Checklist – An input/output traceability matrix



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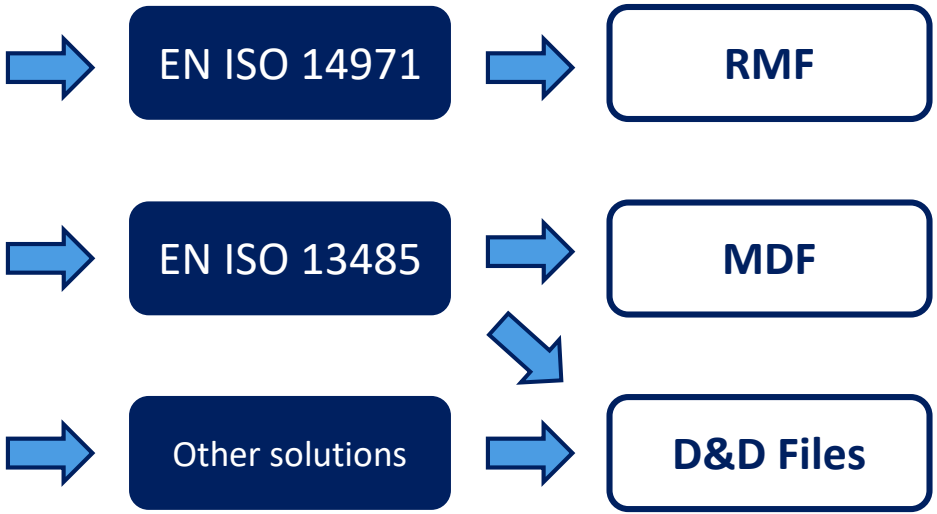
Ensuring that Conformity Evidence is Linked

8 Design & Manufacturing ERs

- ❑ Chemical and physical properties
- ❑ Infection and microbial contamination
- ❑ Manufacturing and environmental properties
- ❑ Devices which are instruments or apparatus with a measuring function
- ❑ Protection against radiation
- ❑ Requirements for medical devices connected to or equipped with an energy source
- ❑ Requirements for devices for self-testing
- ❑ Information supplied by the manufacturer



Priority Areas for Review

ERC

RMF

PESR

Labeling

PMS

- ❑ Has applicability been correctly determined?
- ❑ Is non-applicability appropriately justified?
- ❑ Are the solutions applied current or obsolete?
- ❑ Are the solutions applied ‘fit for purpose’?
- ❑ Is the solution applied appropriately described?
- ❑ Is the specific documented evidence described?
- ❑ Is the ERC a ‘controlled’ document?

Priority Areas for Review

- ERC
- **RMF**
- PESR
- Labeling
- PMS

- ❑ Transition to EN ISO 14971:2019?
- ❑ Has a device-specific, compliant RMP been established?
- ❑ Have all reasonably foreseeable hazards been identified?
- ❑ Have both ‘normal’ and ‘in fault’ condition hazards been considered?
- ❑ Have the severity of false positive, false negative and invalid test results been appropriately determined?
- ❑ Has an appropriate overall benefit-risk analysis been performed?

Priority Areas for Review

ERC

RMF

PESR

Labeling

PMS

- ❑ Are all applicable analytical and clinical performance characteristics supported by the PESR?
- ❑ Is there sufficient traceability to the original data (e.g. references to study protocol/report)?
- ❑ Is there an appropriate rationale or justification for methodology, including sample sizes, used?
- ❑ Are results appropriately described?
- ❑ Where relevant, is applicability of clinical performance data to EU populations sufficiently described?

Priority Areas for Review

- **ERC**
- **RMF**
- **PESR**
- **Labeling**
- **PMS**

- ❑ Is the intended purpose/use commensurate with the ERC, RMF and PESR?
- ❑ Are summaries of all analytical and clinical performance characteristics described?
- ❑ Are all contraindications, warnings, precautions and limitations described consistent with the ERC, RMF and PESR?
- ❑ Are there any deficiencies regarding grammar, spelling, translations?

Priority Areas for Review

ERC

RMF

PESR

Labeling

PMS

- ❑ Has a PMS process been established?
- ❑ Are PMS activities commensurate with the nature of the device?
- ❑ Has the RMF been updated to reflect real-world experience with the device?

Change impact

Changes in qualification/classification

Changes to qualification

- Clarification of certain purposes (e.g. impairments)
- Information concerning predisposition to a medical condition or disease
- To predict treatment response or reactions (CDx)
- IVD MDSW (MDCG 2019-11)

Changes to classification

- Classification changes to all devices

Increased Notified Body involvement means greater need to **justify** the level of evidence

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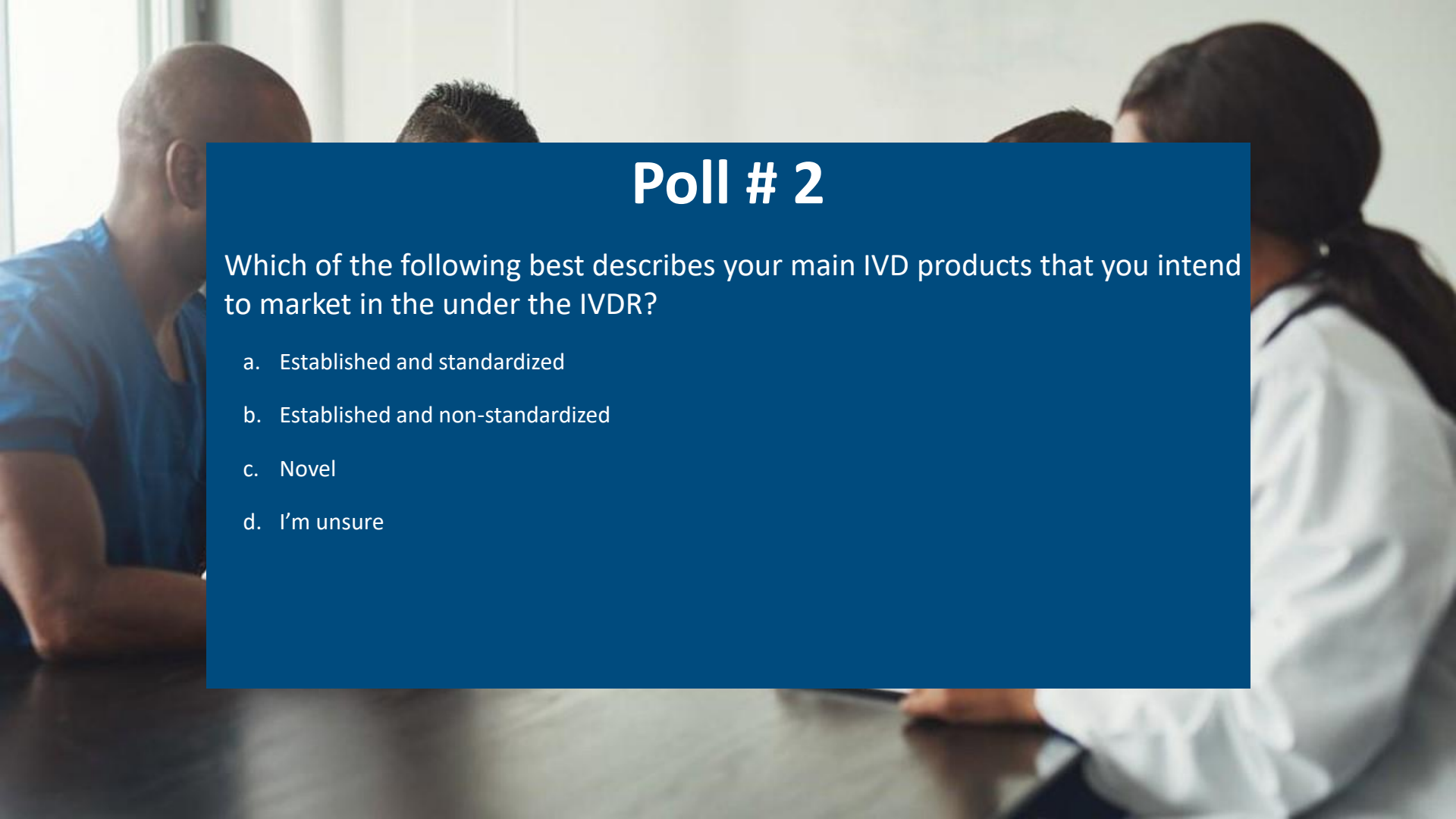

Poll # 2

Which of the following best describes your main IVD products that you intend to market in the under the IVDR?

a. Established and standardized

b. Established and non-standardized

c. Novel

d. I’m unsure

IVD Novelty

Established and Standardized

- An international standard or accepted reference materials (e.g. WHO) of the analyte exists, and
- More than one commercial test is available, and
- Test produces equivalent results for the analyte regardless of the method/manufacturer. Equivalence will depend on the device, intended purpose/use, risk class, and authority view.

Established and Non-Standardized

- Tests have clinical guidelines and/or consensus for their use and/or medically accepted as gold standard
- More than one commercial test available
- While international reference materials may exist, results obtained from different IVDs might not be used interchangeably

Novel

- A device which incorporates technology (the analyte, technology or test platform) not previously used in diagnostics and not continuously available on the European Community market during the previous three years, or;
- An existing device which is being used for a new intended purpose for the first time
- Not established or standardized

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Source: GHTF/ GHTF/SG5/N7:2012 Clinical Evidence for IVD medical devices – Scientific Validity Determination and Performance Evaluation, Definitions from MDEG New and Emerging Technologies Task Force

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Technical Documentation File Structure for Systems

Closed System

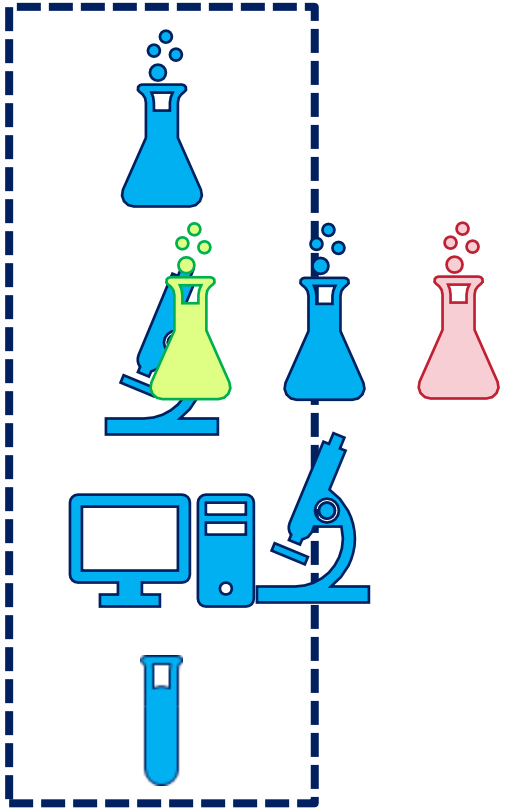
Reagent
Reagent Product
Calibrator
Control Material
Kit

Instrument
Apparatus
Piece of Equipment

Software

Specimen Receptacle

System



TDF # 1

RMF | PER

TDF # 2

RMF | PER

TDF # 3

RMF | PER

TDF # 4

RMF | PER

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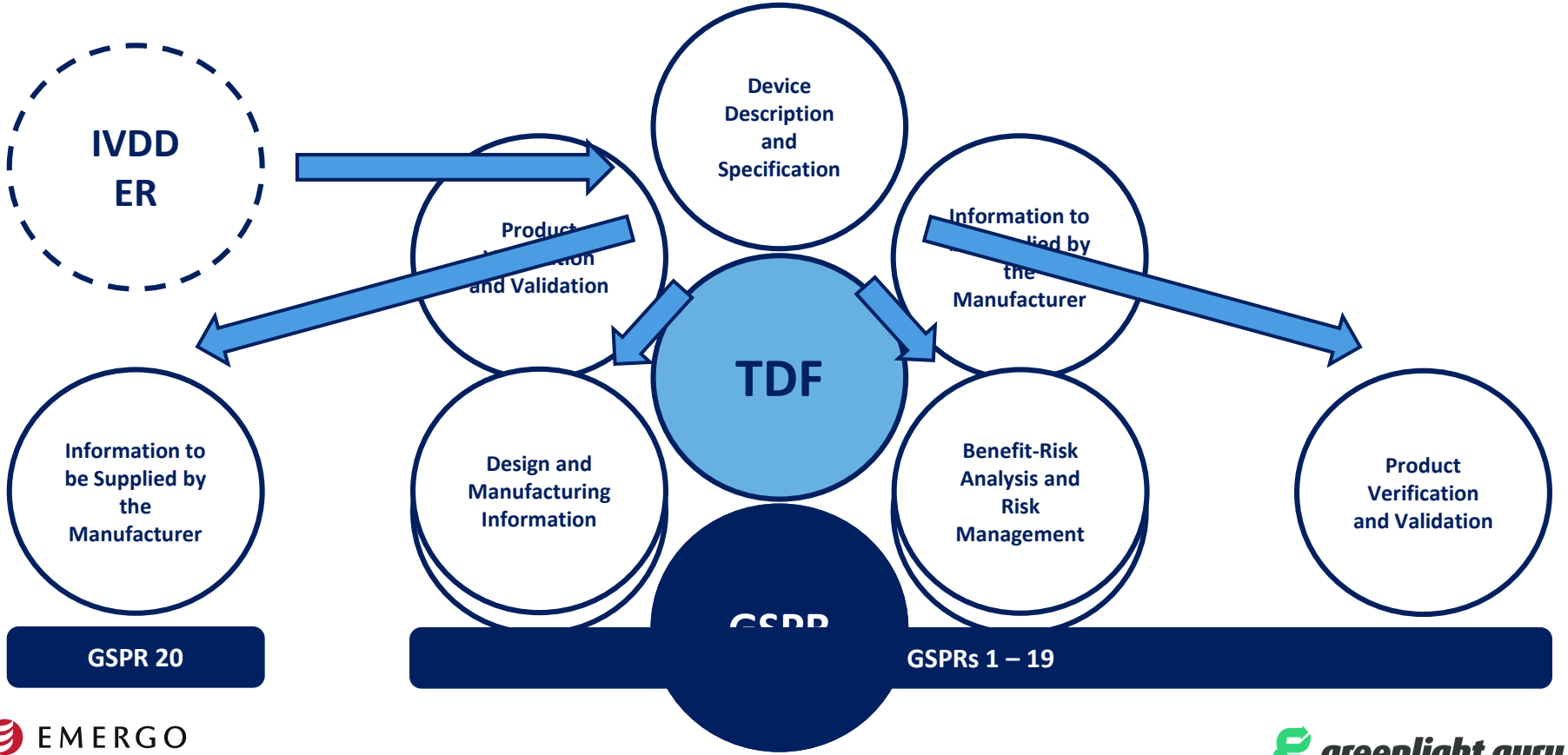
Planning the pathway forward

Technical Documentation File Compilation (Annex II)



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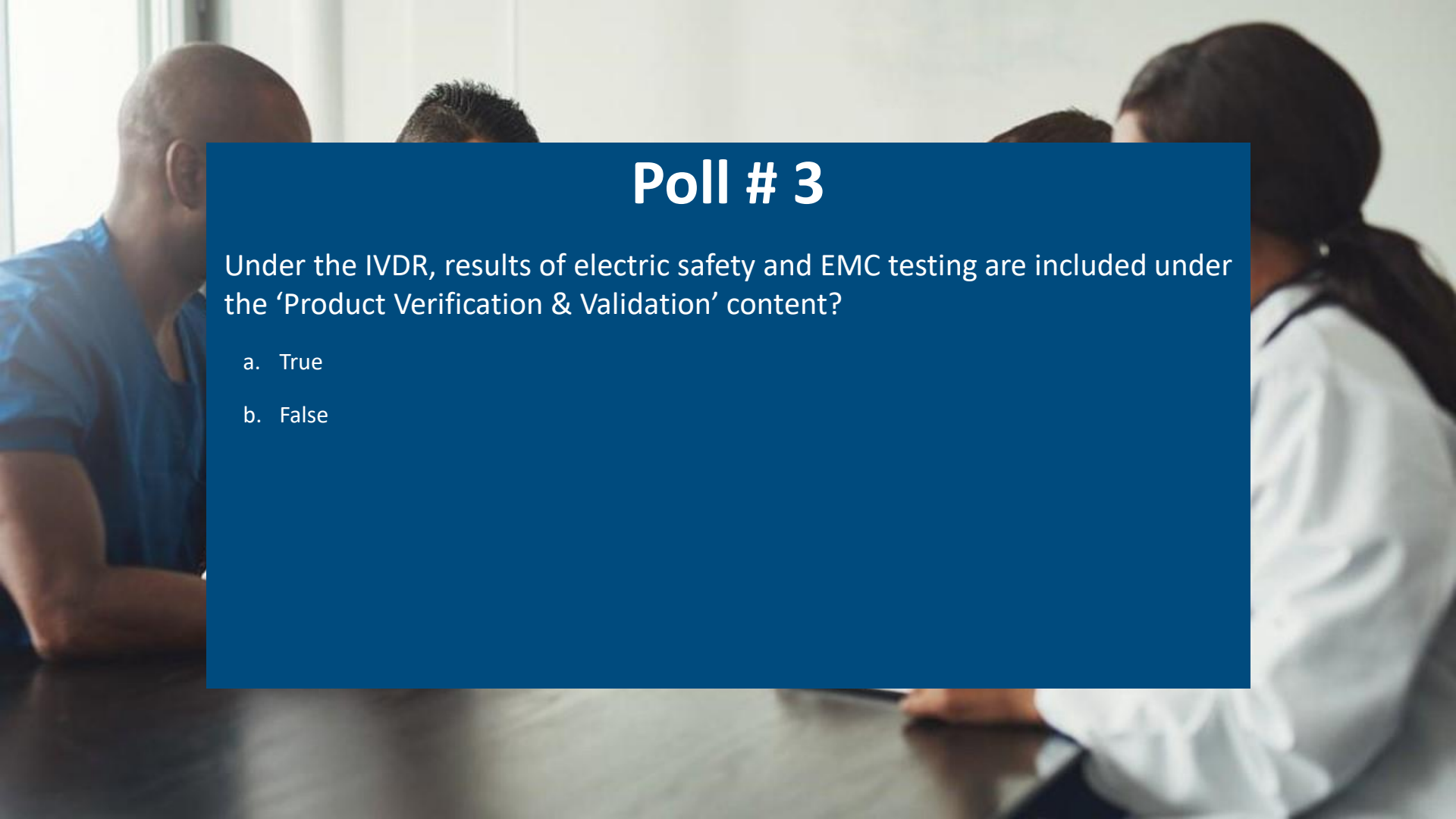


Poll # 3

Under the IVDR, results of electric safety and EMC testing are included under the ‘Product Verification & Validation’ content?

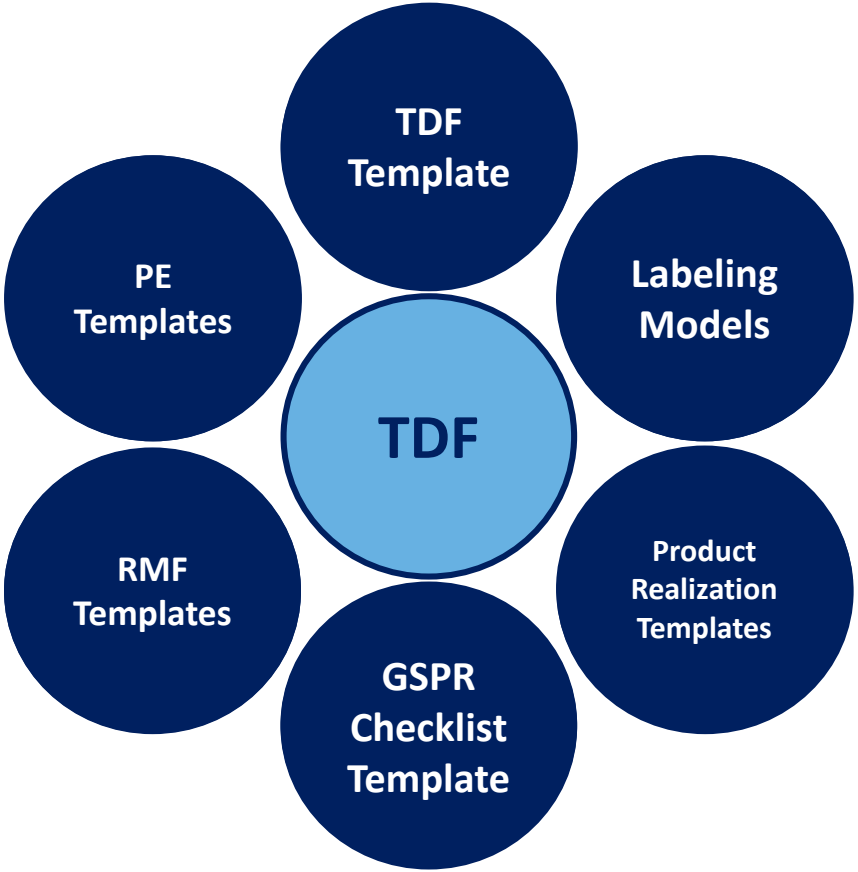
a. True

b. False

Technical Documentation File Compilation (Annex II)

QMS Elements

- ❑ Strategy for QMS Compliance
- ❑ Labeling Controls
- ❑ Product Realization Controls
- ❑ Risk Management System
- ❑ Performance Evaluation Process
- ❑ Other Relevant V&V Processes



Summary Technical Documentation (STED)

IVD Marketing Authorization Table of Contents (IVD MA ToC)

Compliant Other / Custom Solutions

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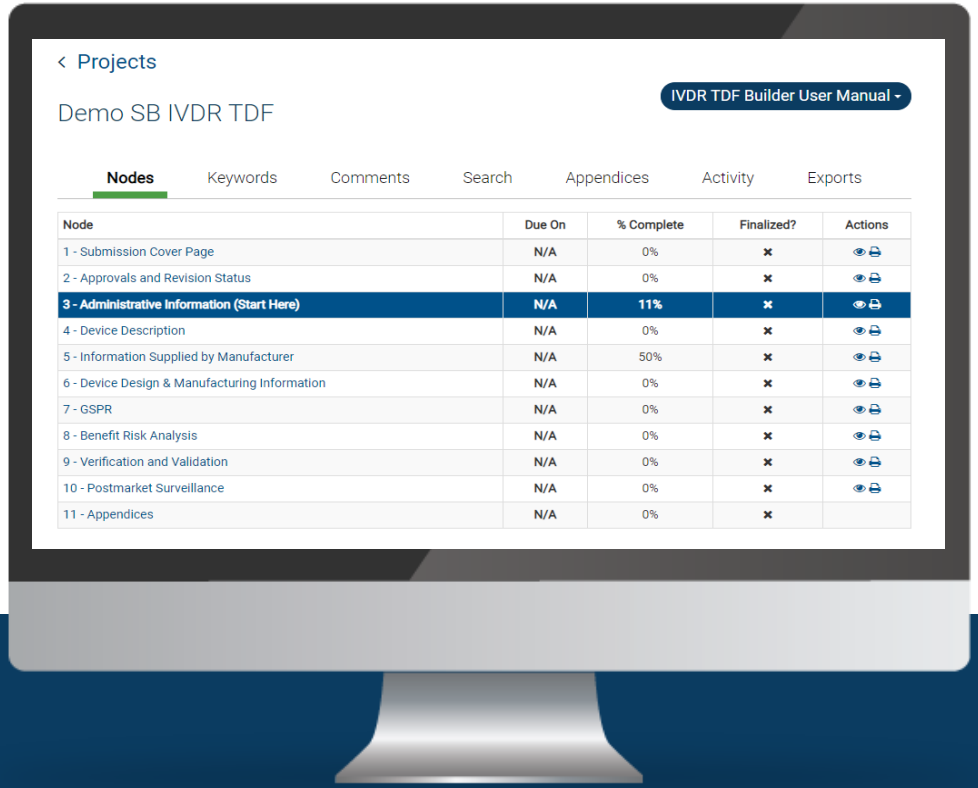
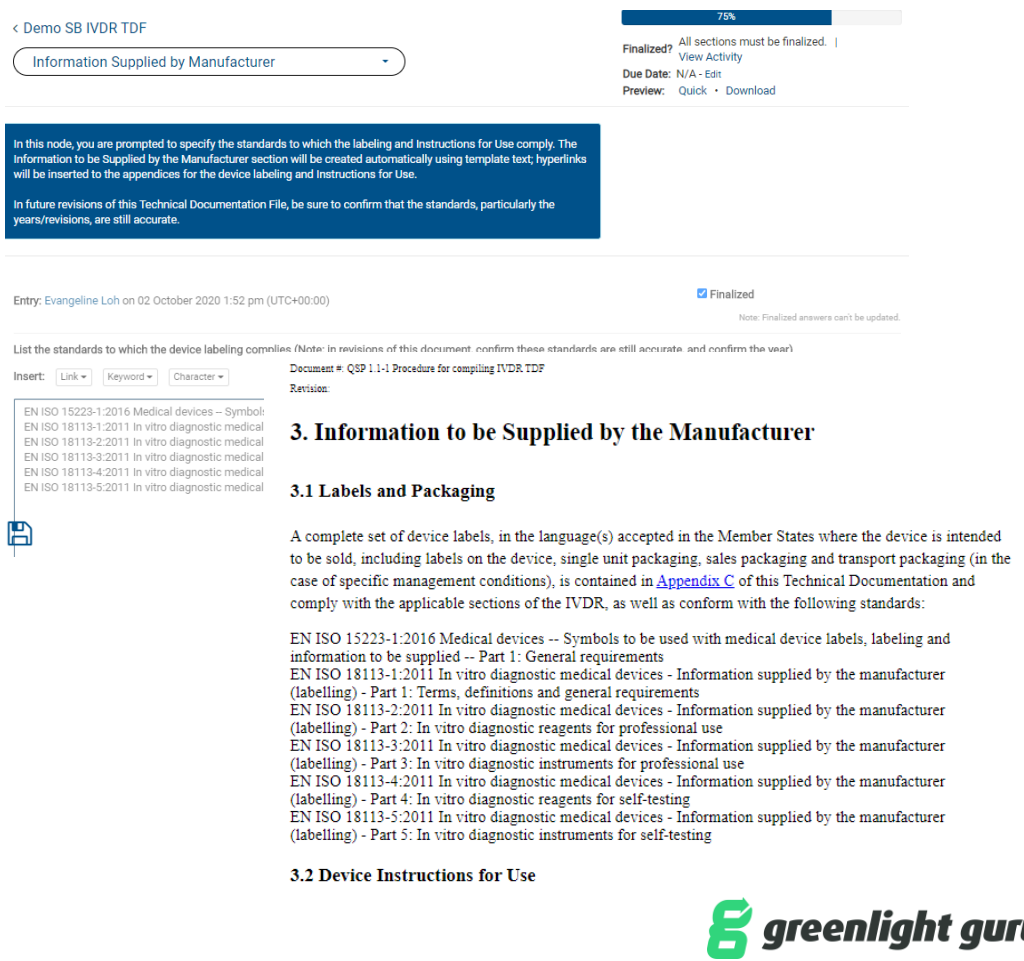
RAMS SB IVDR TDF

- Guides the user in the compilation of their IVDR TDF
- User directed to provide Appendices or QMS location references for supporting data
- Project management features
- Finished product is a hyperlinked, bookmarked PDF that can be maintained in RAMS SB (“living” document)



RAMS SB IVDR TDF

- Extensive template text built into the project
- Minimizes user effort, reduces errors and standardizes content
- Some nodes require very little user input, e.g. Node 4 – Information Supplied by the Manufacturer
- User simply needs to review, confirm and accept auto-populated content



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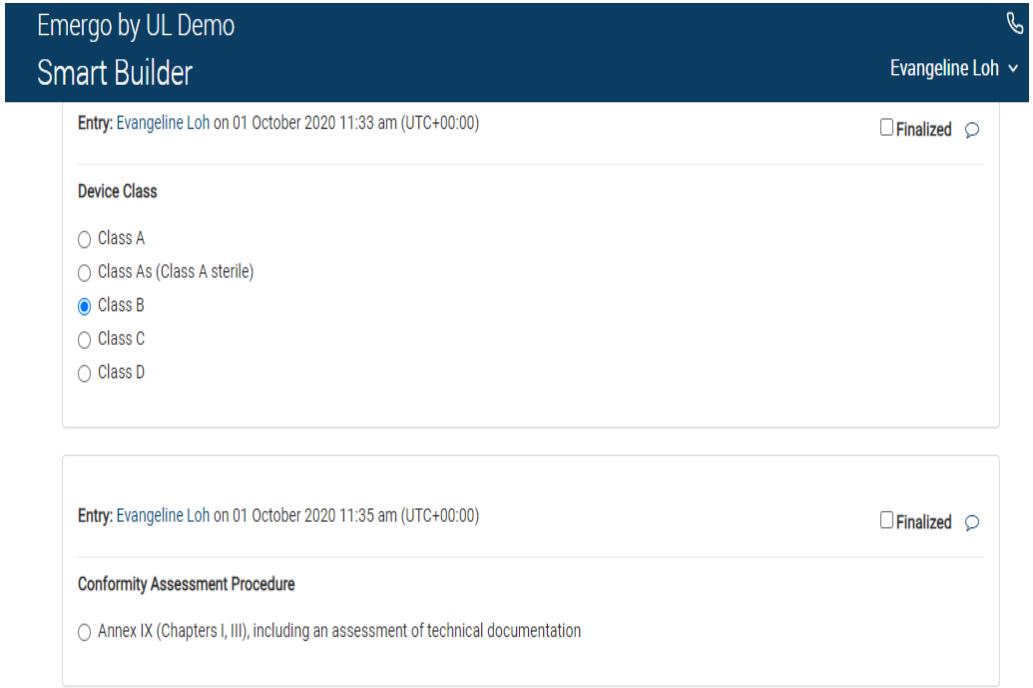
RAMS SB IVDR TDF

- In order to streamline the compilation process, there is logic built into many of the questions within the IVDR TDF Builder
- Responses will enable or disable related questions based on responses provided
- Reduces errors and standardizes approaches



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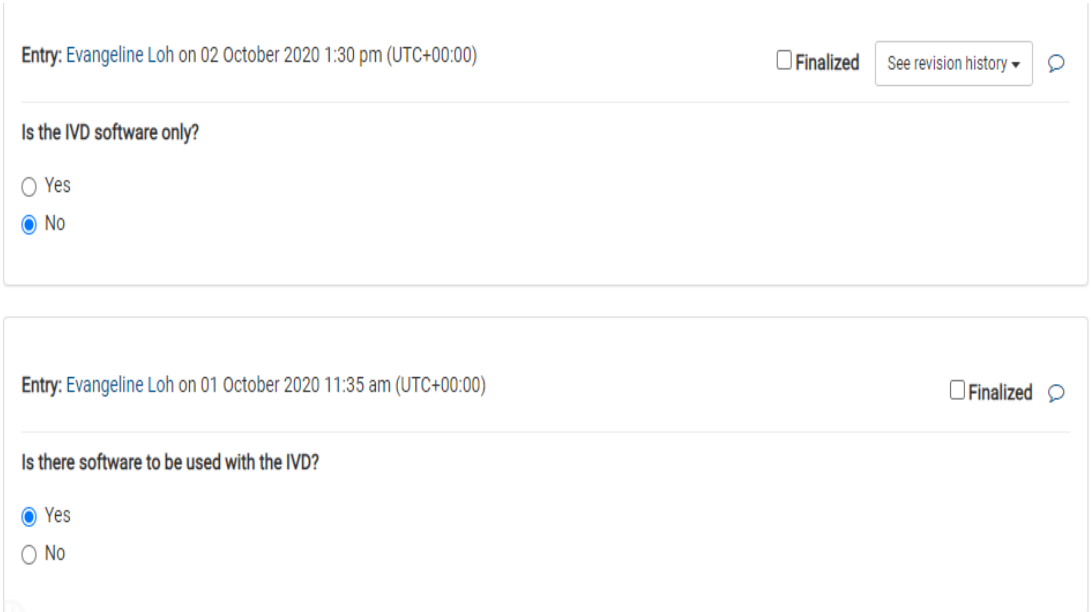

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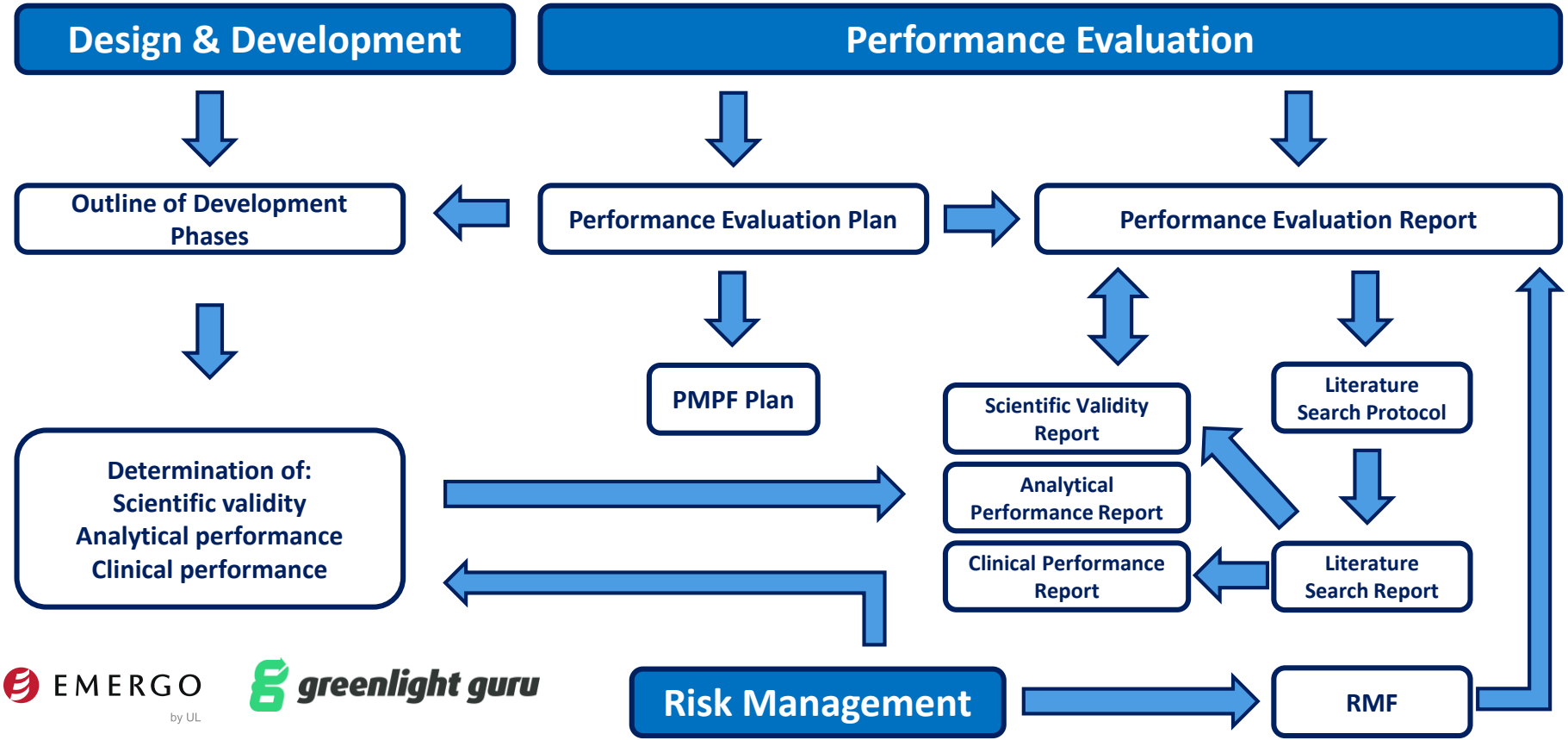
Technical Documentation File Compilation (Annex II)



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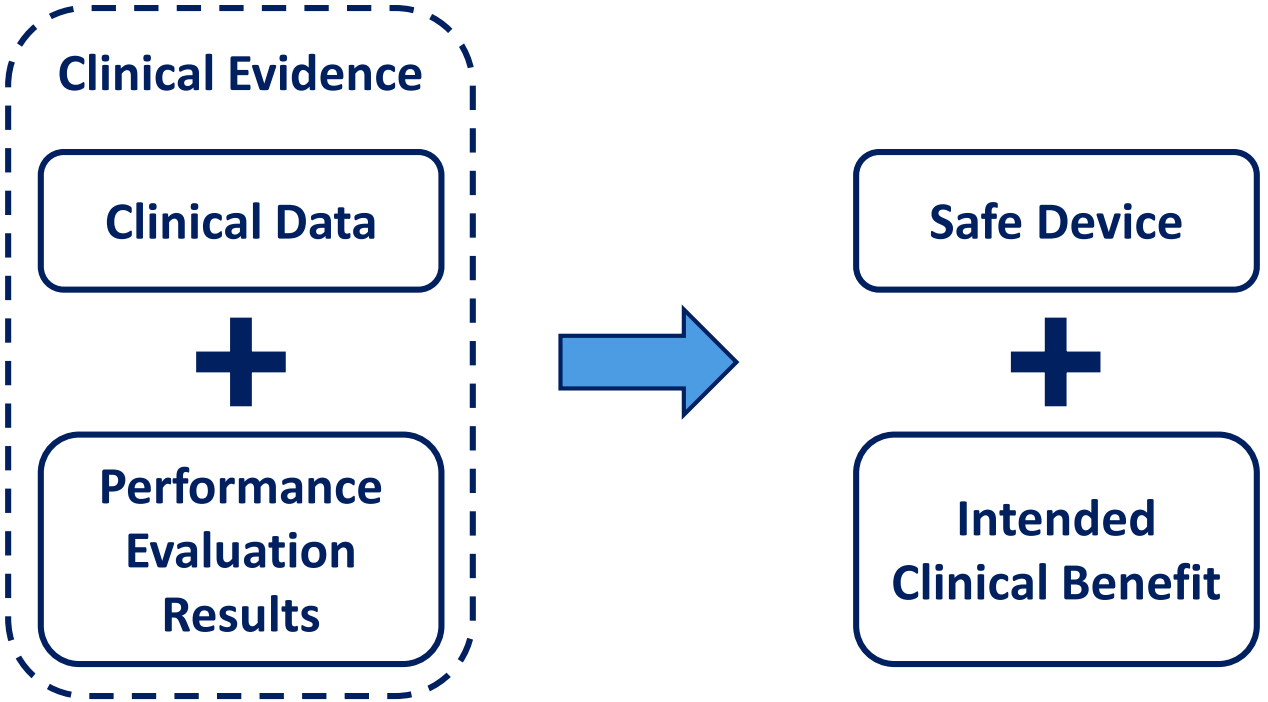
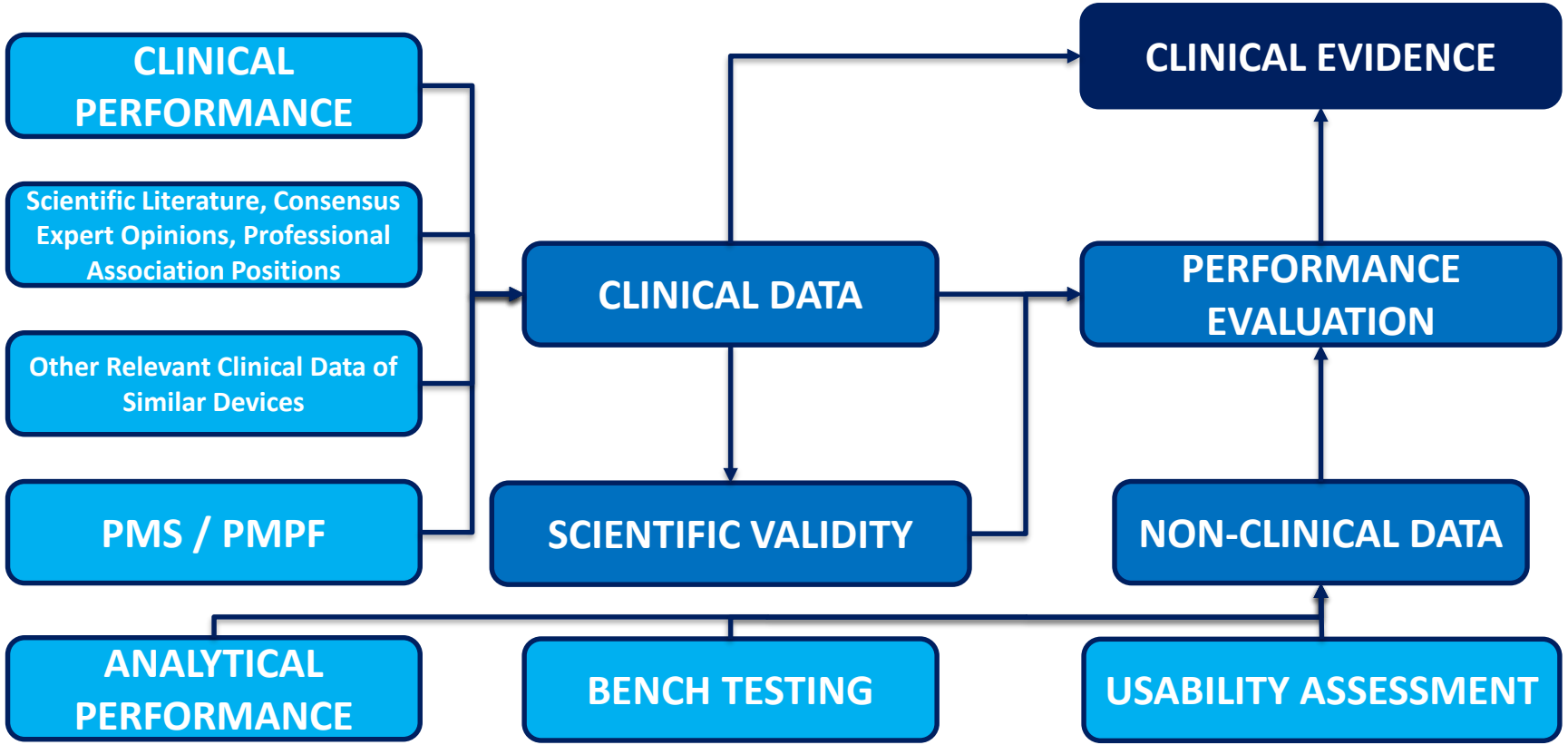
Evidence evaluation

Clinical Evidence

- Specify and justify the level of clinical evidence to demonstrate GSPR conformity
- Appropriate in view of the characteristics of the device and its intended purpose



Clinical Evidence



Clinical Evidence

Scientific Validity

- ❑ Devices measuring the same analyte or marker
- ❑ Scientific literature
- ❑ Consensus expert opinions/positions
- ❑ Proof of concept studies
- ❑ Clinical performance studies

Analytical Performance

- ❑ Analytical performance studies

Clinical Performance

- ❑ Clinical performance studies
- ❑ Scientific literature
- ❑ Published experience

Section 4.5.4, Annex VII

The Notified Body's assessment of the performance evaluation as referred to in Annex XIII shall cover:

…

- Validity of equivalence claimed in relation to other devices, the demonstration of equivalence; the suitability and conclusions data from equivalent and similar devices

Clinical Evidence – Literature Searches

Scientific Validity | **Clinical Performance** | **State of the Art**

PICO Term	Scientific Validity	Clinical Performance	State of the Art
Patient	Patients suffering from [Clinical condition or disease]	Patients suffering from [Clinical condition or disease]	Patients suffering from [Clinical condition or disease]
Intervention	[Detection of specific analyte]	[Diagnosis with the subject device or equivalent or similar device]	[Diagnostic purpose]
Control/Comparator	N/A	N/A	[Control/Comparator technologies]
Outcome	Correlation	[Device-specific outcomes]	Benefit, Clinical Risks, Alternatives, History

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Clinical Evidence – Equivalency/Similarity

MDR

- ❑ Clinical

  e.g. Used for same clinical condition or purpose

- ❑ Technical

  e.g. Similar principles of operation

- ❑ Biological

  e.g. Uses the same materials or substances in contact with same human tissue or body fluids for a similar kind of duration or contact

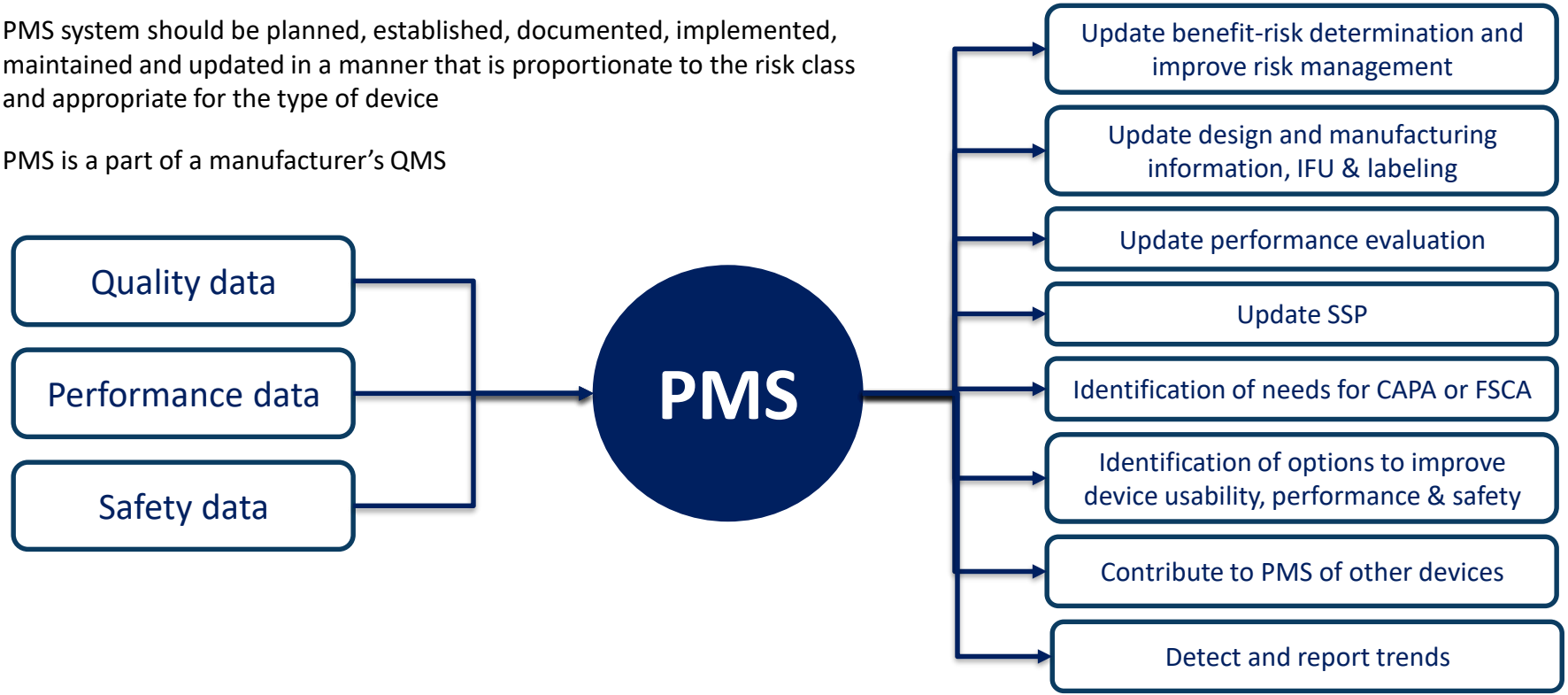
IVDR

- ❑ Clinical
- ❑ Technology / Methodology
- ❑ Design
- ❑ Operating conditions
- ❑ Performance characteristics
- ❑ Composition

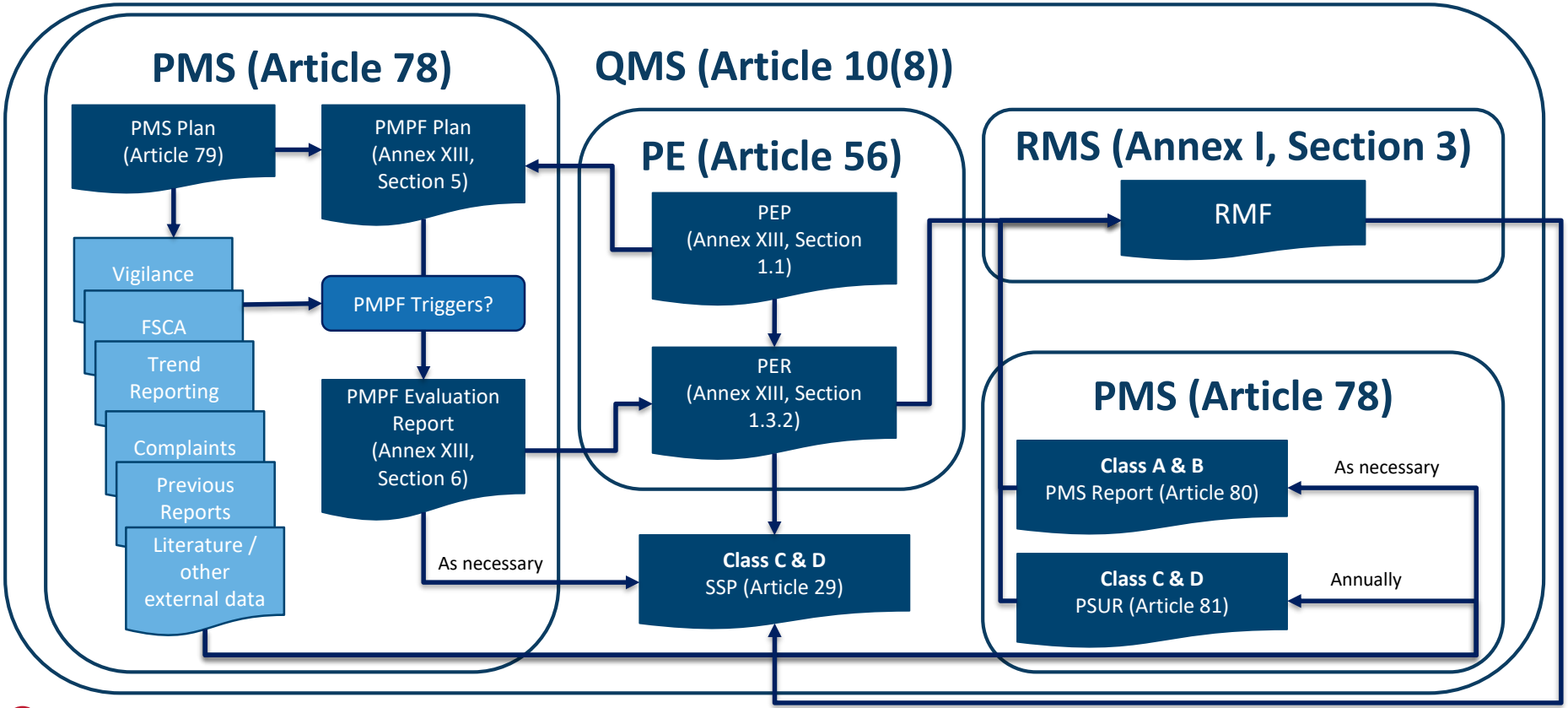
Planning ongoing compliance

Post-Market Surveillance (PMS)

- PMS system should be planned, established, documented, implemented, maintained and updated in a manner that is proportionate to the risk class and appropriate for the type of device
- PMS is a part of a manufacturer's QMS



PMS / PMPF



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PMPF Triggers – Trend Reporting

- Establishing thresholds for statistically significant changes in trends (frequency and severity) and benefit-risk analysis