IVDR – Performance Evaluation

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Agenda

- Regulatory Requirements
- Review Experiences & General pain points
- Lessons Learned

Performance Evaluation Regulatory Requirements

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Performance Evaluation – new concept?

IVDD – 98/79/EC

- Annex III.3, 11th indent

adequate performance evaluation data showing the performances claimed by the manufacturer ….; such data should originate from studies in a clinical or other appropriate environment or from relevant biographical references

- Annex VIII

Plan: *"stating in particular the purpose, scientific, technical or medical grounds, scope of the evaluation and number of devices concerned"*

- Article 1 (e): *'device for performance evaluation' means any device intended by the manufacturer to be subject to one or more performance evaluation studies in laboratories for medical analyses or in other appropriate environments outside his own premises*

IVDR 2017/746

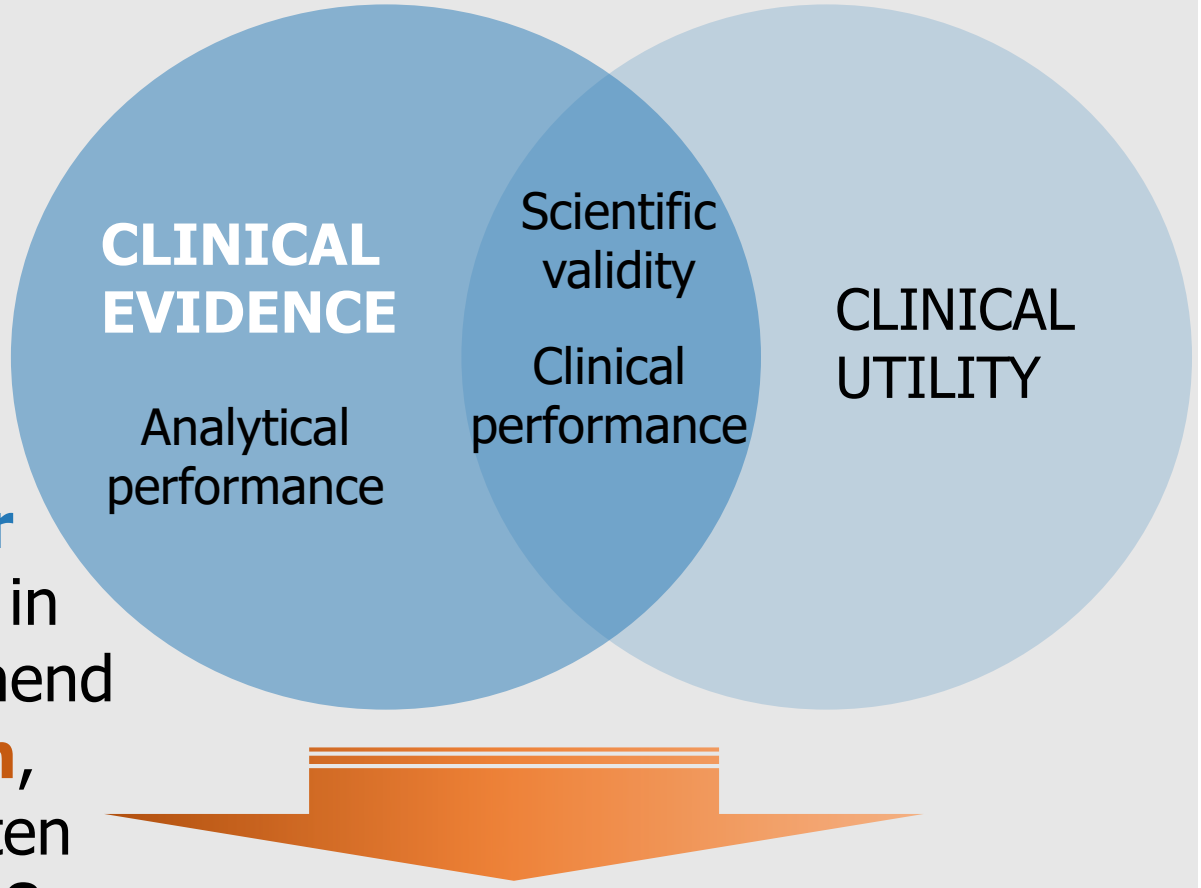
Chapter VI
Clinical evidence, performance evaluation and performance studies
(Article 56 to Article 77)

Annex XIII & Annex XIV

Clinical Evidence

= Scientific Validity + Analytical Performance + Clinical Performance

= klinische Daten und die Ergebnisse der Leistungsbewertung zu einem Produkt, die in quantitativer und qualitativer Hinsicht ausreichend sind, **um qualifiziert beurteilen zu können**, ob das Produkt **sicher ist** und den angestrebten **klinischen Nutzen** bei **bestimmungsgemäßer Verwendung** nach Angabe des Herstellers erreicht



***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*

Clinical Benefit

Clinical benefit of an IVD

=

Accurate medical information

≠

Final clinical outcome

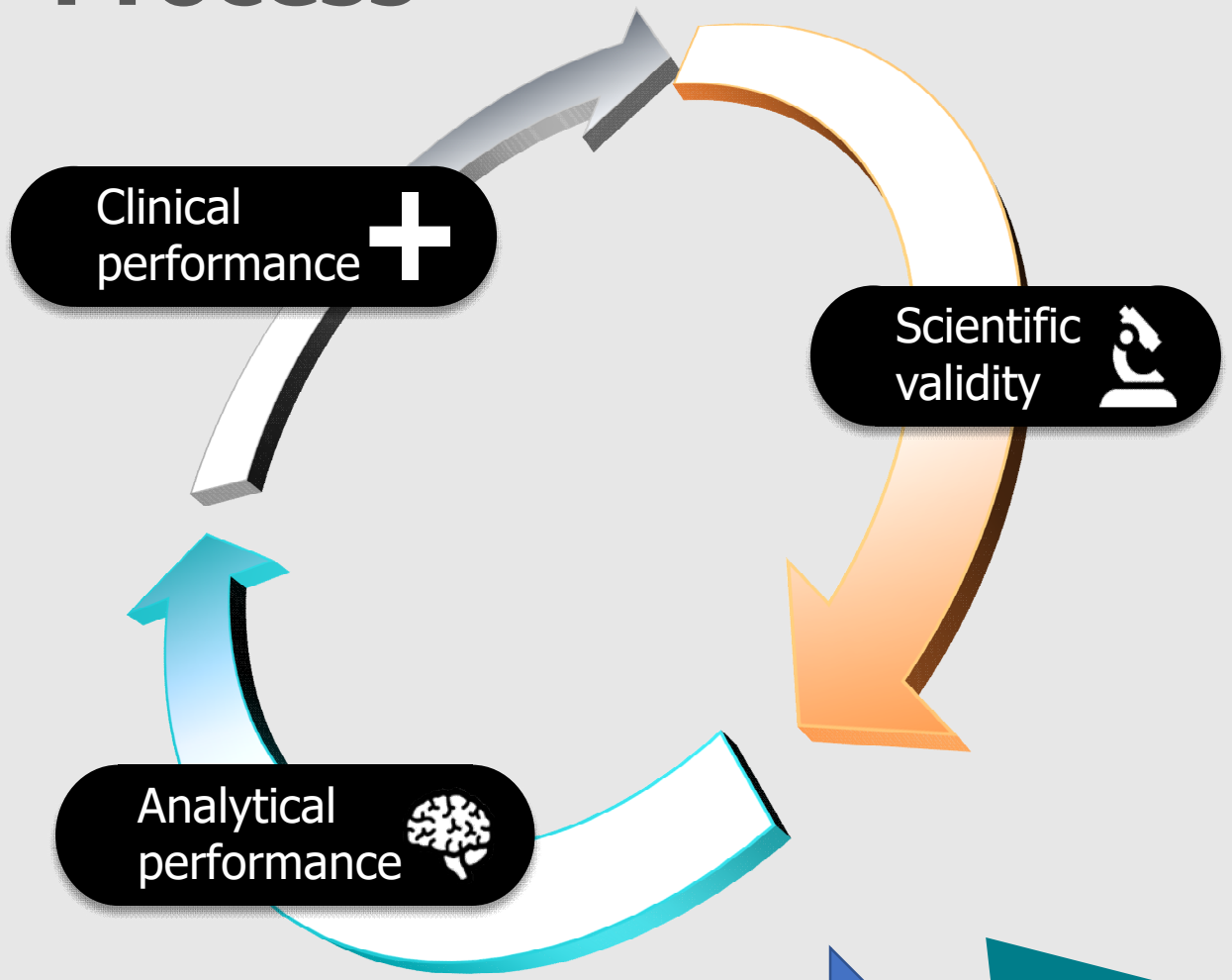
≠ Clinical Utility

Reference: IVDR Preamble (64)

Es sollte darauf hingewiesen werden, dass das Konzept des klinischen Nutzens bei *In-vitro*-Diagnostika sich grundlegend von demjenigen unterscheidet, das bei Arzneimitteln oder therapeutischen Medizinprodukten gilt, da der Nutzen von *In-vitro*-Diagnostika in der Bereitstellung angemessener medizinischer Informationen über Patienten liegt, die gegebenenfalls im Vergleich zu medizinischen Informationen bewertet werden, die aus der Verwendung anderer diagnostischer Optionen und Techniken resultieren, wohingegen das endgültige klinische Ergebnis für den Patienten von weiteren diagnostischen und/oder therapeutischen Optionen, die zur Verfügung stehen könnten, abhängt.

Performance Evaluation - Process

- Ref Annex II & **Annex XIII**
- Done according to a **Performance Evaluation Plan**
- Collated as a **Performance Evaluation Report**

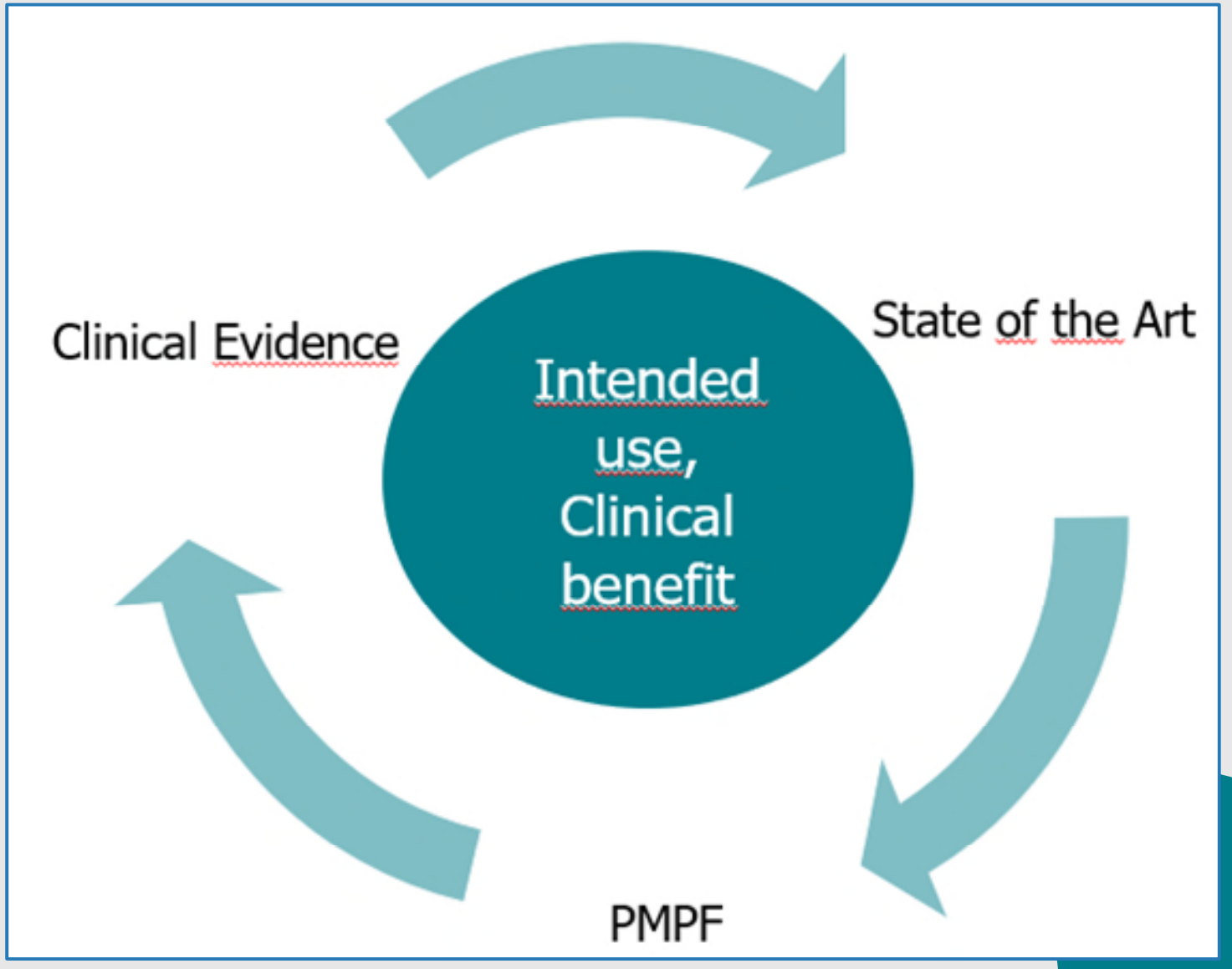


Continuous during life-time of the device > PMPF

Performance Evaluation – Life Time Approach

Annex II
Technical Documentation
Annex III
Technical Documentation on **PMS**

Annex XIII
Part A
Performance Evaluation &
Performance Studies
Part B
PMPF



Intended Use = Intended Purpose

- IFU is the governing document of each TD!
- All IFU claims need to be supported by evidence and reviewed on continuous benefit/risk acceptability
  - ✓ **Intended Purpose/Use**
  - ✓ Intended target population
  - ✓ Intended specimen type(s)
  - ✓ Stability claims
  - ✓ Scientific Validity
  - ✓ Analytical performance
  - ✓ Clinical performance
  - ✓ Limitations & contraindications
  - ✓ **State of the Art**

- **Performance Evaluation**
- **Risk Management**
- **PMS**

How much should be in there?

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)*

"Its 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)*

Performance Evaluation
Review Experiences & General Pain Points

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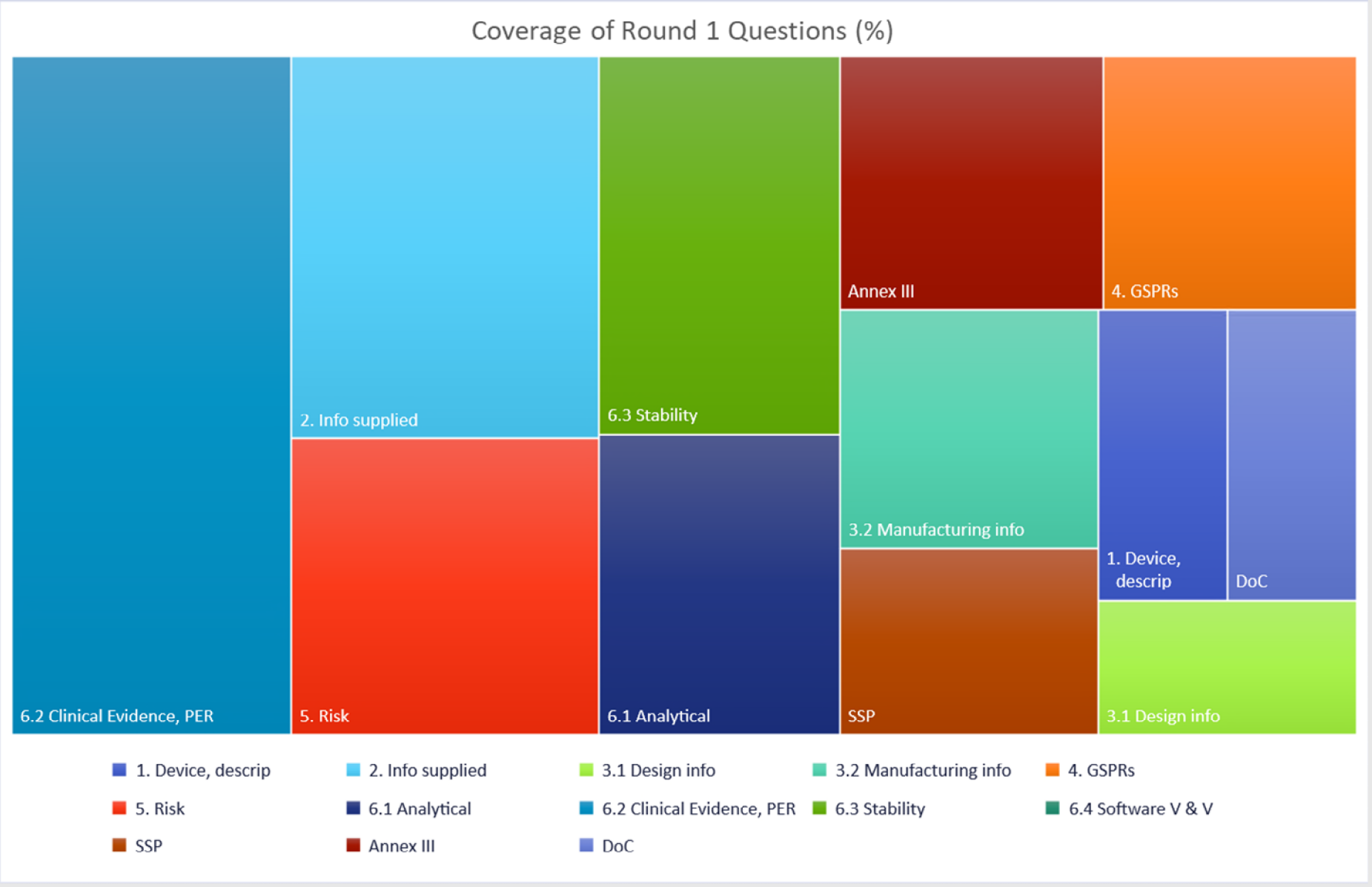
Summary of Questions raised



Questions cover all aspects of Annex II, III, XIII

Majority Clinical Evidence

↓

Analytical & Stability

↓

Information supplied

↓

Risk Management

↓

SSP & DoC

TD – General considerations

A complete and well-organized file decreases 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"

TD – General considerations

IVDR is very prescriptive

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


Guidance - MDCG endorsed documents and other guidance

~~Deutsch~~ English

This page provides a range of documents to assist stakeholders in applying Regulation (EU) 2017/745 on medical devices (MDR) and Regulation (EU) 2017/746 (IVDR) on in vitro diagnostic medical devices. The majority of documents on this page are endorsed by the Medical Device Coordination Group (MDCG) in accordance with Article 105 of the MDR and Article 99 of the IVDR. They are drafted in collaboration with interested parties represented in the various groups and denominated by the following format: "MDCG Year-Number-revision".

The documents on this page are not legally binding. They present a common understanding of how the MDR and IVDR should be applied in practice aiming at an effective and harmonised implementation of the legislation.

MDCG work in progress

Ongoing guidance documents

Use IVDR terminology!

Verify Consistency across your file

- ✓ Consider DoC & SSP as applicable

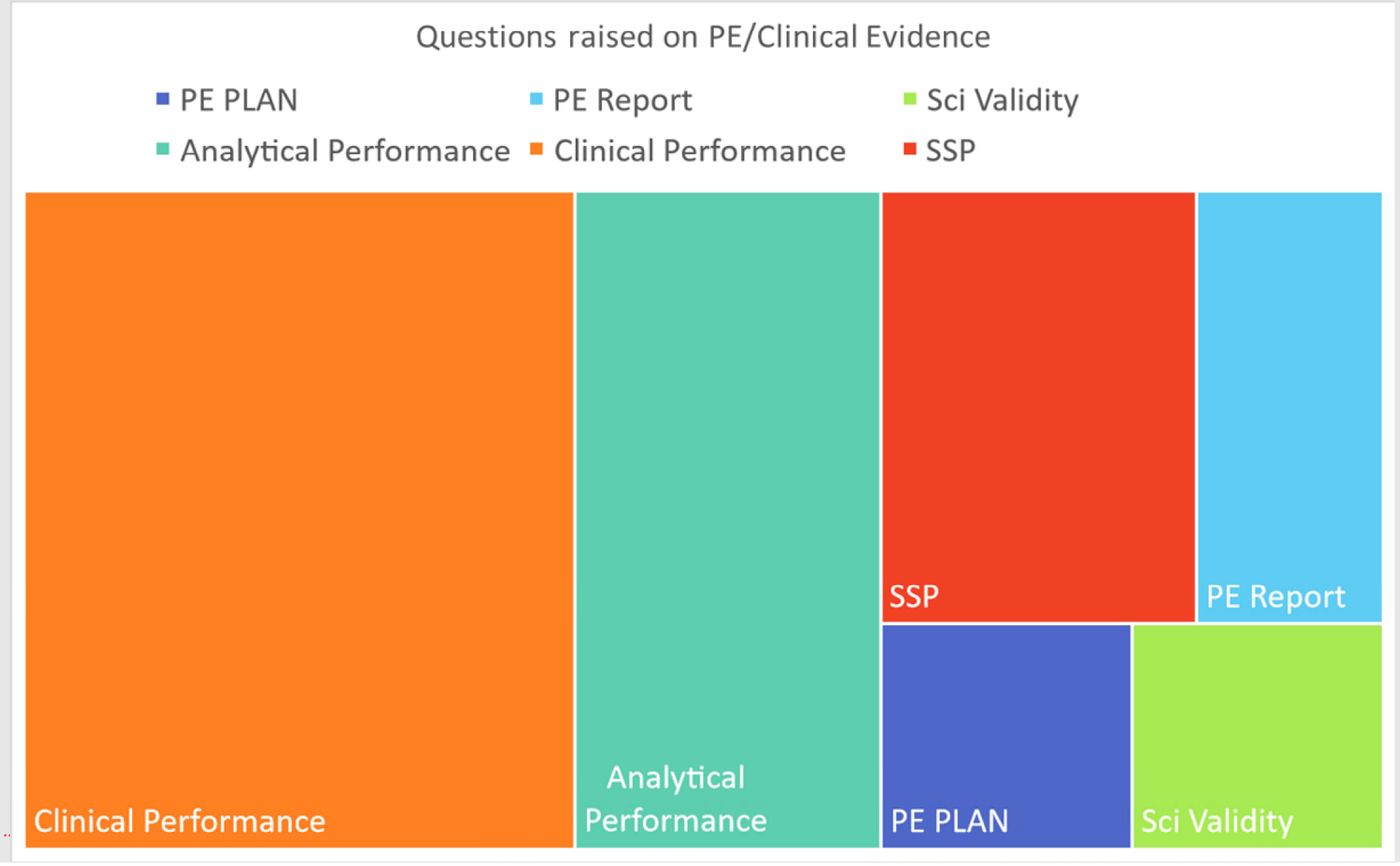
Consistency Check by „impartial" colleagues?

TD – General considerations

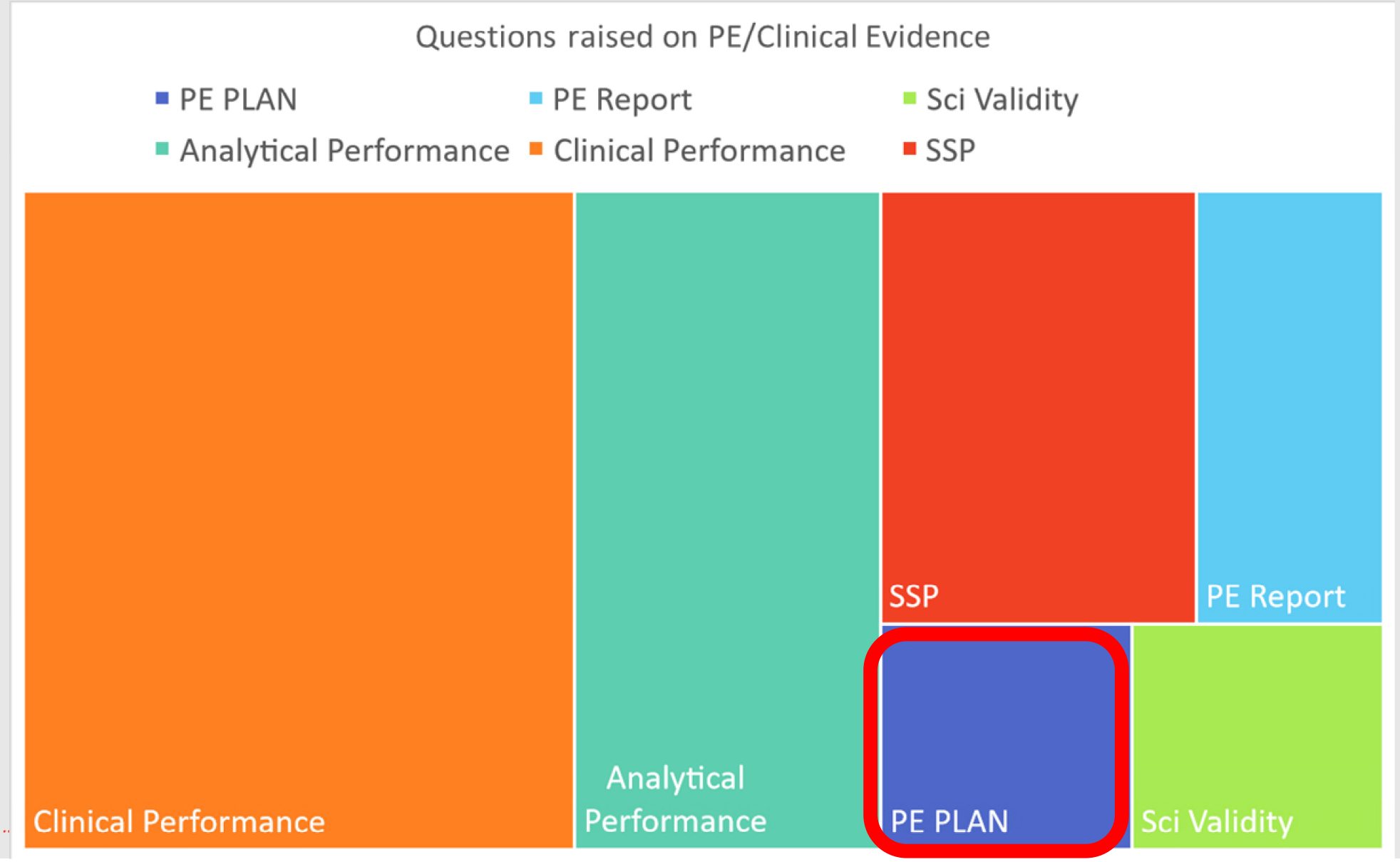
Performance Evaluation proportionate to risk class & intended purpose

- ✓ What is needed for a Control, Calibrator?
- ✓ What is needed for Software?
- ✓ What is needed for an Instrument?
- ✓ What is needed for a test/assay – NGS assay vs ELISA?
- ✓ What is needed for different user
  - ✓ *professional , near-patient, self test*

Summary of questions raised on Performance Evaluation



Summary of questions raised on Performance Evaluation



Majority of identified deficiencies

Annex XIII 1.1 Performance Evaluation Plan (PEP)

Indent 9

— a description of the state of the art, including an identification of existing relevant standards, CS, guidance or best practices documents;

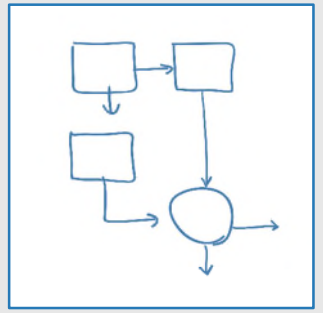
Indent 10

— an indication and specification of parameters to be used to determine, based on the state of the art in medicine, the acceptability of the benefit-risk ratio for the intended purpose or purposes and for the analytical and clinical performance of the device;

Indent 13

— the PMPF planning as referred to in Part B of this Annex.

Performance Evaluation Plan



- The aim is to outline the strategy to prove the performance for the **claimed intended purpose**
  - ✓ Poor intended purpose is difficult to prove!
  - ✓ If state of the art is not defined, then a PE strategy cannot be planned to meet it
  - ✓ Devices with broad intended purpose still need to meet PE requirements
    - ➢ E.g., microbiology culture media, Class A sterile specimen receptacles, software, instruments, controls, calibrators
    - ➢ Think carefully about intended purpose then plan a strategy to prove it

Where a device is 'legacy', *what is the "Plan"?*

The PE Plan is HOW you are approaching evaluation of performance today

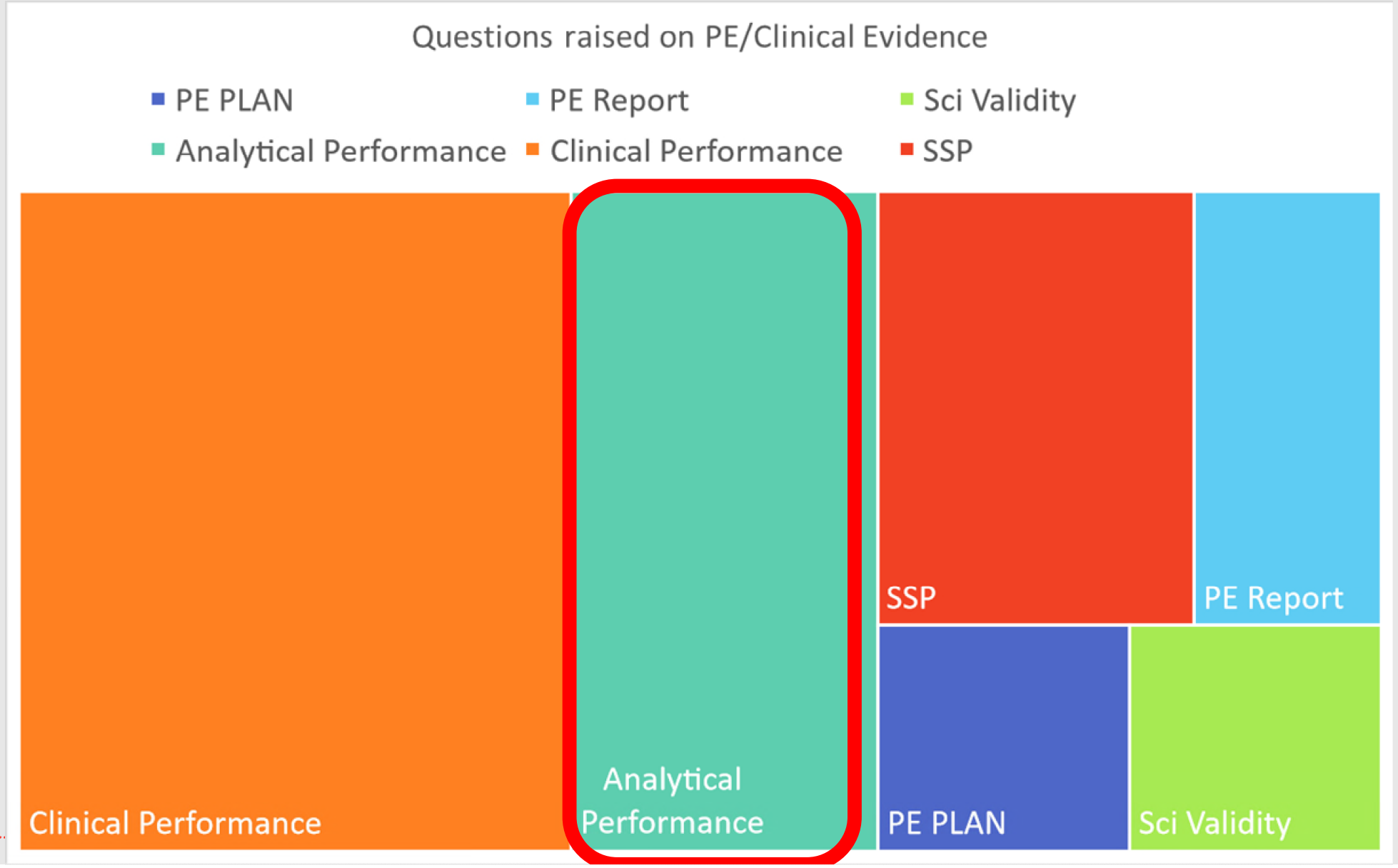
- ➢ It is not an old study protocol!

✓ What is the intended use today? (i.e. what claims are you making?)

✓ What is '*state of the art*' today?

✓ How are you going to draw upon **all** performance information available today?

Summary of questions raised on Performance Evaluation



Analytical Performance Studies

↓

GSPR 9.1 (a)

↓

No CE marked assay and/or no reference measurement procedure available

No other approach

↓

Clinical Performance Studies are required!

↓

State of the Art

1.2.2. Demonstration of the analytical performance

The manufacturer shall demonstrate the analytical performance of the device in relation to all the parameters described in point (a) of Section 9.1 of Annex I, unless any omission can be justified as not applicable.

As a general rule, the analytical performance shall always be demonstrated on the basis of analytical performance studies.

For novel markers or other markers without available certified reference materials or reference measurement procedures, it may not be possible to demonstrate trueness. If there are no comparative methods, different approaches may be used if demonstrated to be appropriate, such as comparison to some other well-documented methods or the composite reference standard. In the absence of such approaches, a clinical performance study comparing performance of the novel device to the current clinical standard practice is required.

Analytical performance shall be demonstrated and documented in the analytical performance report.

Majority of identified deficiencies

Annex II.6.1 Information on analytical performance on the device

Annex XIII 1.2.2 Demonstration of Analytical Performance

- ✓ Consistency to IFU
- ✓ Justify non-applicability
- ✓ Missing studies and/or partial studies to support IFU claims
  - ➢ Interference
  - ➢ Specimen claims

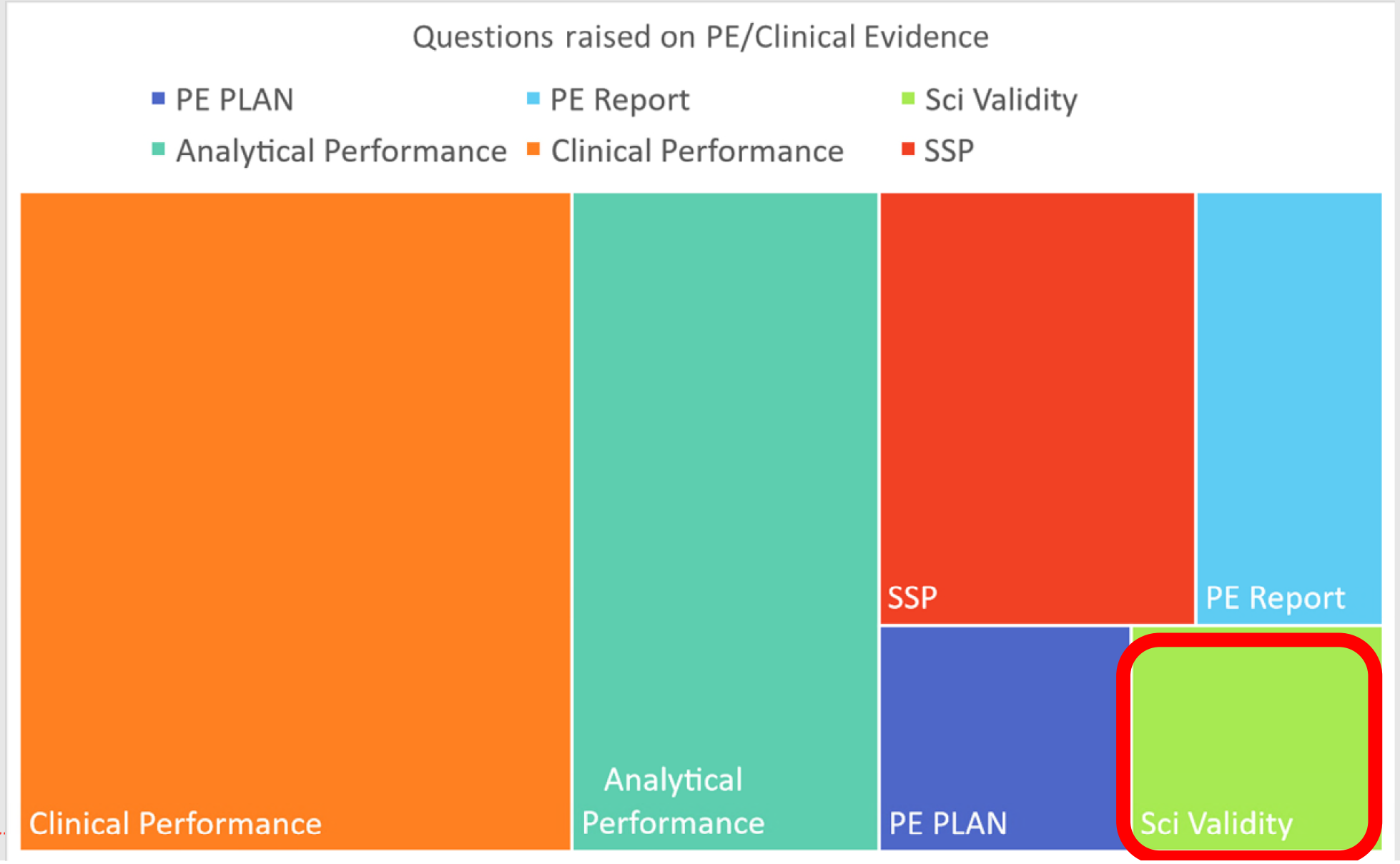
Majority of identified deficiencies

Annex II.6.1 Information on analytical performance on the device

Annex XIII 1.2.2 Demonstration of Analytical Performance

- ✓ Indications which instruments have been used
  - ➢Closed platform
  - ➢Open platform
- ✓Comparison Study
  - ➢Should be CE-marked
  - ➢No CE-marked device available – think about "state of the art"

Summary of questions raised on Performance Evaluation



Scientific Validity

Annex VII
NB shall review the methodology for Literature searching

The literature review must be 'systematic'

GHTF/SG5/N7:2012 (Clinical Evidence for IVD medical devices – Scientific Validity Determination and Performance Evaluation)
MEDDEV 2.7/1 revision 4 (Clinical Evaluation: A Guide for Manufacturers and NBs)

1.2.1. Demonstration of the scientific validity

The manufacturer shall demonstrate the scientific validity based on one or a combination of the following sources:

— relevant information on the scientific validity of devices measuring the same analyte or marker;

— scientific (peer-reviewed) literature;

— consensus expert opinions/positions from relevant professional associations;

— results from proof of concept studies;

— results from clinical performance studies.

The scientific validity of the analyte or marker shall be demonstrated and documented in the scientific validity report.

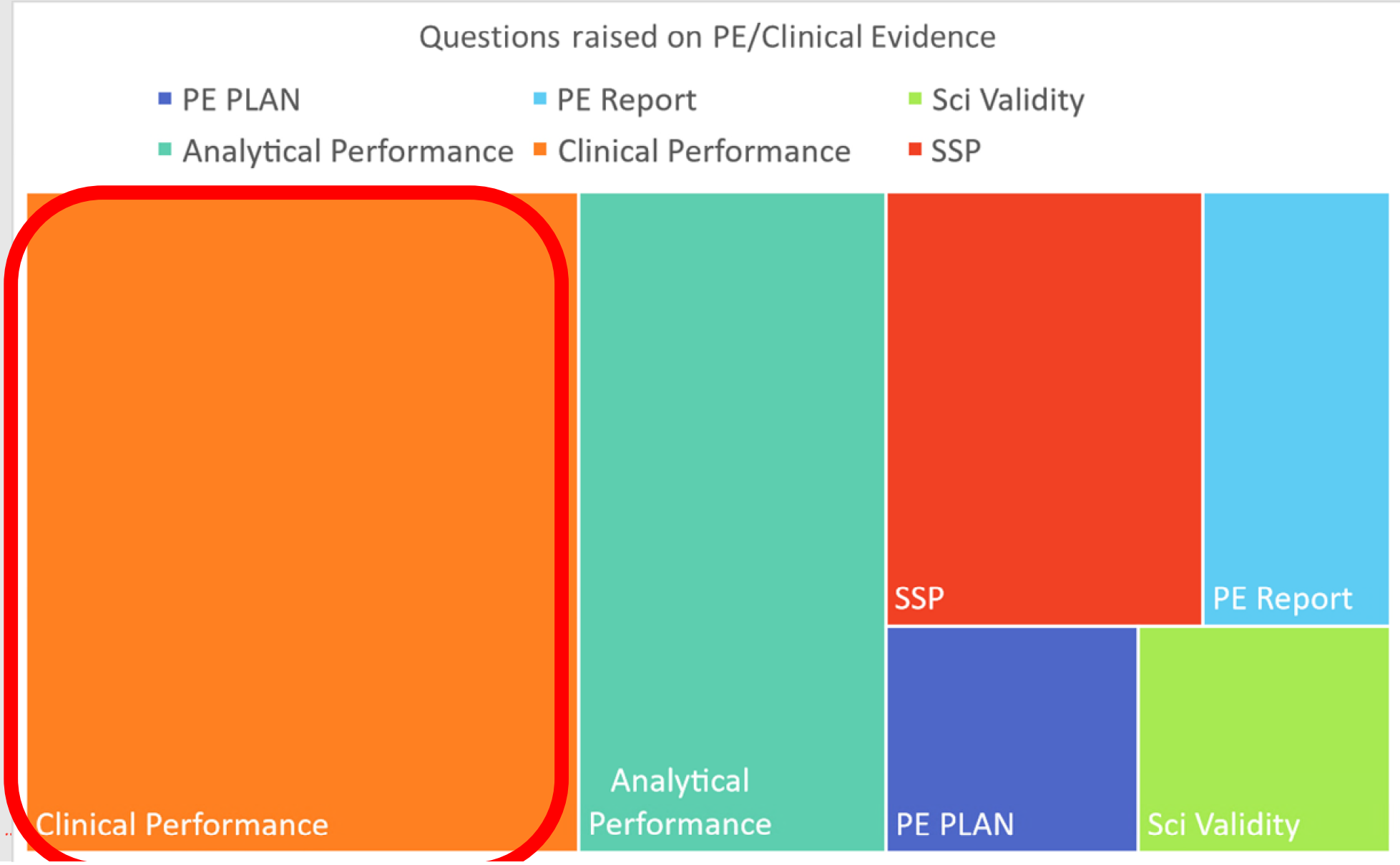
Scientific Validity

Reference to articles

- ✓ NB needs a summary/rationale of why the articles are relevant / appropriate
  - references in the articles are useful
  - request copies of the articles
- ✓ Linkage to the **intended purpose**

Consider favorable and non favorable data

Summary of questions raised on Performance Evaluation



Clinical Performance

GSPR 9.1. (b)

General confusion HOW to **apply** and **demonstrate** Clinical Performances sources

Justification not doing clinical performance studies

Other sources?

1.2.3. Demonstration of the clinical performance

The manufacturer shall demonstrate the clinical performance of the device in relation to all the parameters described in point (b) of Section 9.1. of Annex I, unless any omission can be justified as not applicable.

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

— clinical performance studies;

— scientific peer-reviewed literature;

— published experience gained by routine diagnostic testing.

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

1. Clinical Performance Studies

Annex XIII Section 2

2.1 Purpose of clinical performance studies
2.2 Ethical considerations
2.3 Methods
    Study design
    Clinical Performance Study Plan
    Clinical Performance Study Report
3. Other performance studies

Reference –
ISO 20916: 2019*

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

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

1. Clinical Performance Studies

Regular gap in Technical Documentation reviews at BSI

- *"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'**

2. Scientific peer-reviewed literature

The majority of legacy devices use this as the main source of clinical performance

Supported by IVDD performance data as a source of "other sources of clinical data" data

!

Review literature to support clinical performance of the specific device

not equal to literature review to demonstrate scientific validity

2. Scientific peer-reviewed literature

Using publications with own device!

Support clinical performance claims?

Support Medical application?

Support State of the Art?

(ii) its function (e.g. screening, monitoring, diagnosis or aid to diagnosis, prognosis, prediction, companion diagnostic);

(iii) the specific information that is intended to be provided in the context of:

— a physiological or pathological state;

— congenital physical or mental impairments;

— the predisposition to a medical condition or a disease;

— the determination of the safety and compatibility with potential recipients;

— the prediction of treatment response or reactions;

— the definition or monitoring of therapeutic measures;

GSPR 20.4.1. (c) links to Annex II 1.1 (c)

3. Published experience gained by routine diagnostic testing

"Published"

- Made available to the public with an identifiable source

"Routine diagnostic testing"

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

➢ Examples

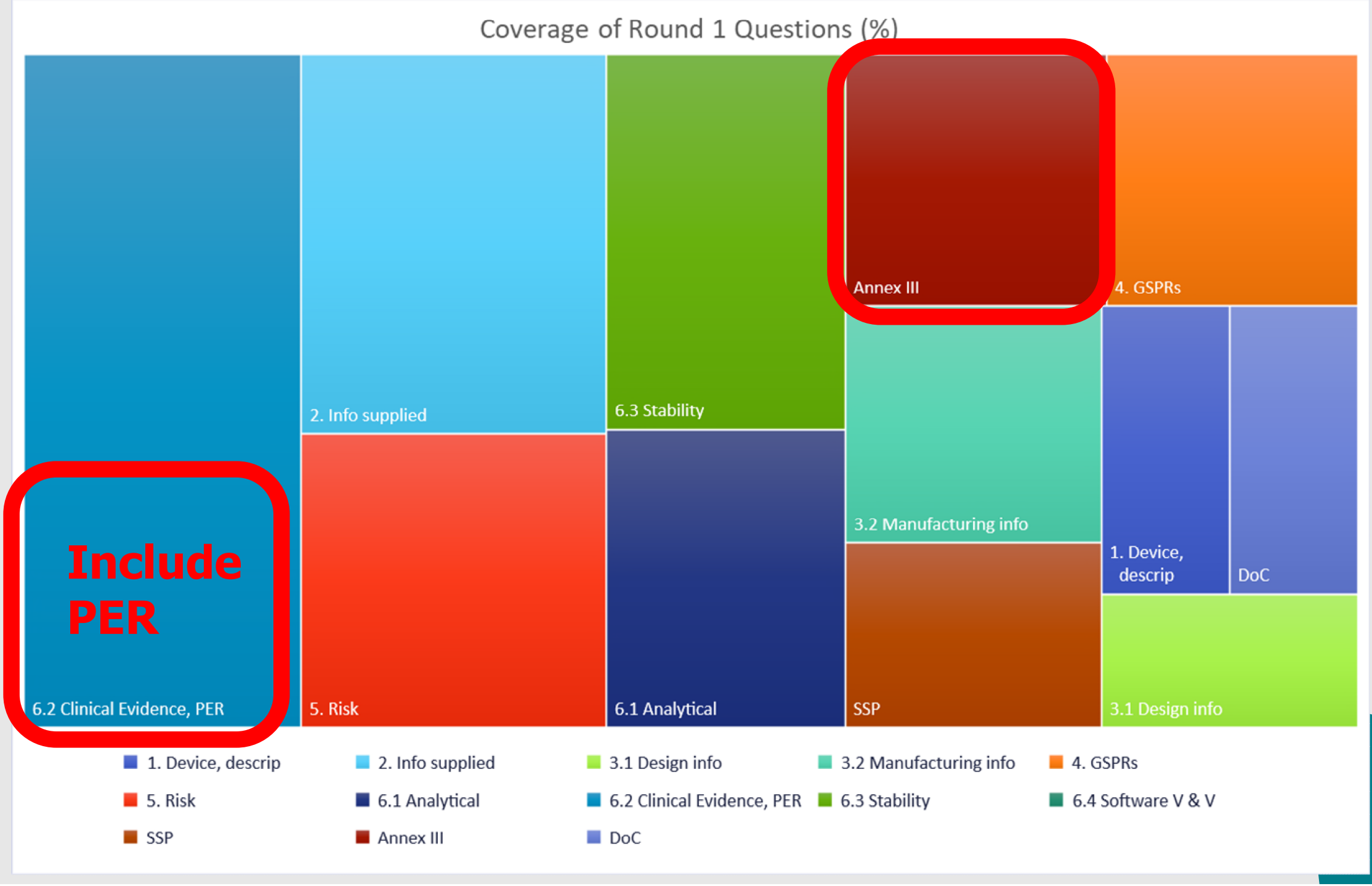
✓ Data from proficiency testing or external quality assurance (EQA) schemes

➢ Demonstrated accurate measurements have been achieved with the device when used according to its intended purpose over many years

Majority of identified deficiencies

- Clinical performance claims (historic data) match the device under review today
- Clinical performance data supporting different use setting (e.g. professional vs NPT vs self test)
- Justification/s not being provided when certain studies have not been performed
- Clinical Performance Data used do not support IFU data/claims
  - Target population, medical application, specimen types
- If used, literature search methodology

PMPF approach?


Coverage of Round 1 Questions (%)
Include PER
6.2 Clinical Evidence, PER
2. Info supplied
5. Risk
6.3 Stability
6.1 Analytical
Annex III
4. GSPRs
3.2 Manufacturing info
SSP
1. Device, descrip
DoC
3.1 Design info
1. Device, descrip
2. Info supplied
3.1 Design info
3.2 Manufacturing info
4. GSPRs
5. Risk
6.1 Analytical
6.2 Clinical Evidence, PER
6.3 Stability
6.4 Software V & V
SSP
Annex III
DoC

Technical Documentation on PMS Annex III

Art 78, 79, 80, 81

Initial certification

Surveillance

ANNEX III

TECHNICAL DOCUMENTATION ON POST-MARKET SURVEILLANCE

The technical documentation on post-market surveillance to be drawn up by the manufacturer in accordance with Articles 78 to 81 shall be presented in a clear, organised, readily searchable and unambiguous manner and shall include in particular the elements described in this Annex.

1. The post-market surveillance plan drawn up in accordance with Article 79.

   The manufacturer shall prove in a post-market surveillance plan that it complies with the obligation referred to in Article 78.

— a PMPF plan as referred to in Part B of Annex XIII, or a justification as to why a PMPF is not applicable.

2. The PSUR referred to in Article 81 and the post-market surveillance report referred to in Article 80.

Majority of identified deficiencies

- PMS Plan does not cover all elements of Annex III a) and b)
  - ✓ IVDR is very prescriptive!
- Scope of PMS Plan is not clear
  - ✓ Which devices/groups are covered?
  - ✓ IVDR does not spell out to have ONE plan for individual devices
  - ✓ Be proportionate!
  - ✓ All risk class specifics need to be covered?

1. For each device manufacturers shall plan, establish, document, implement, maintain and update a post-market surveillance system in a manner that is proportionate to the risk class and appropriate for the type of device. That system shall be an integral part of the manufacturer's quality management system referred to in Article 10(8).

Majority of identified deficiencies

- Justification not doing a PMPF
  - ✓ Triggers & indicators for doing PMPF need to be spelled out

4. PMPF shall be understood to be a continuous process that updates the performance evaluation referred to in Article 56 and Part A of this Annex and shall be specifically addressed in the manufacturer's post-market surveillance plan. When conducting PMPF, the manufacturer shall proactively collect and evaluate performance and relevant scientific data from the use of a device which bears the CE marking and is placed on the market or put into service within its intended purpose as referred to in the relevant conformity assessment procedure, with the aim of confirming the safety, performance and scientific validity throughout the expected lifetime of the device, of ensuring the continued acceptability of the benefit-risk ratio and of detecting emerging risks on the basis of factual evidence.

Links to SSP Article 29 2(f)
Links to PEP & PER Annex XIII 1.1 & 1.3.2

Performance Evaluation Lessons Learned

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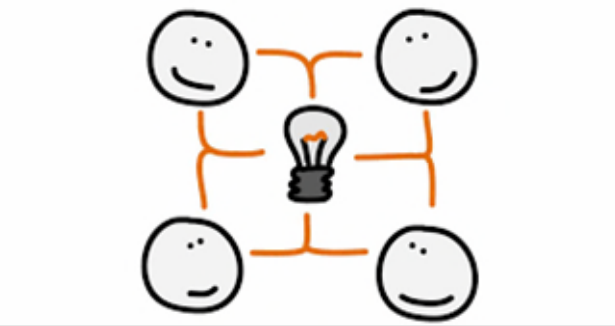
Lessons learned



Performance evaluation

- ✓ All elements shall be included or justified as not applicable
- ✓ Strategy for Performance Evaluation should be planned, even for legacy devices
- ✓ Strategy for demonstrating PE for device families, calibrators, controls, SW, instruments is key

The stated Intended use/purpose is critical for setting the clinical evidence required

Lessons learned

- IFU is the governing document of each TD!
- All IFU claims need to be supported by evidence and reviewed on continuous benefit/risk acceptability
  - ✓ **Intended Purpose/Use**
  - ✓ Intended target population
  - ✓ Intended specimen type(s)
  - ✓ Stability claims
  - ✓ Scientific Validity
  - ✓ Analytical performance
  - ✓ Clinical performance
  - ✓ Limitations & contraindications
  - ✓ **State of the Art**

- **Performance Evaluation**
- **Risk Management**
- **PMS**

Thank you for your attention!