IVDR CE mark – Case Study

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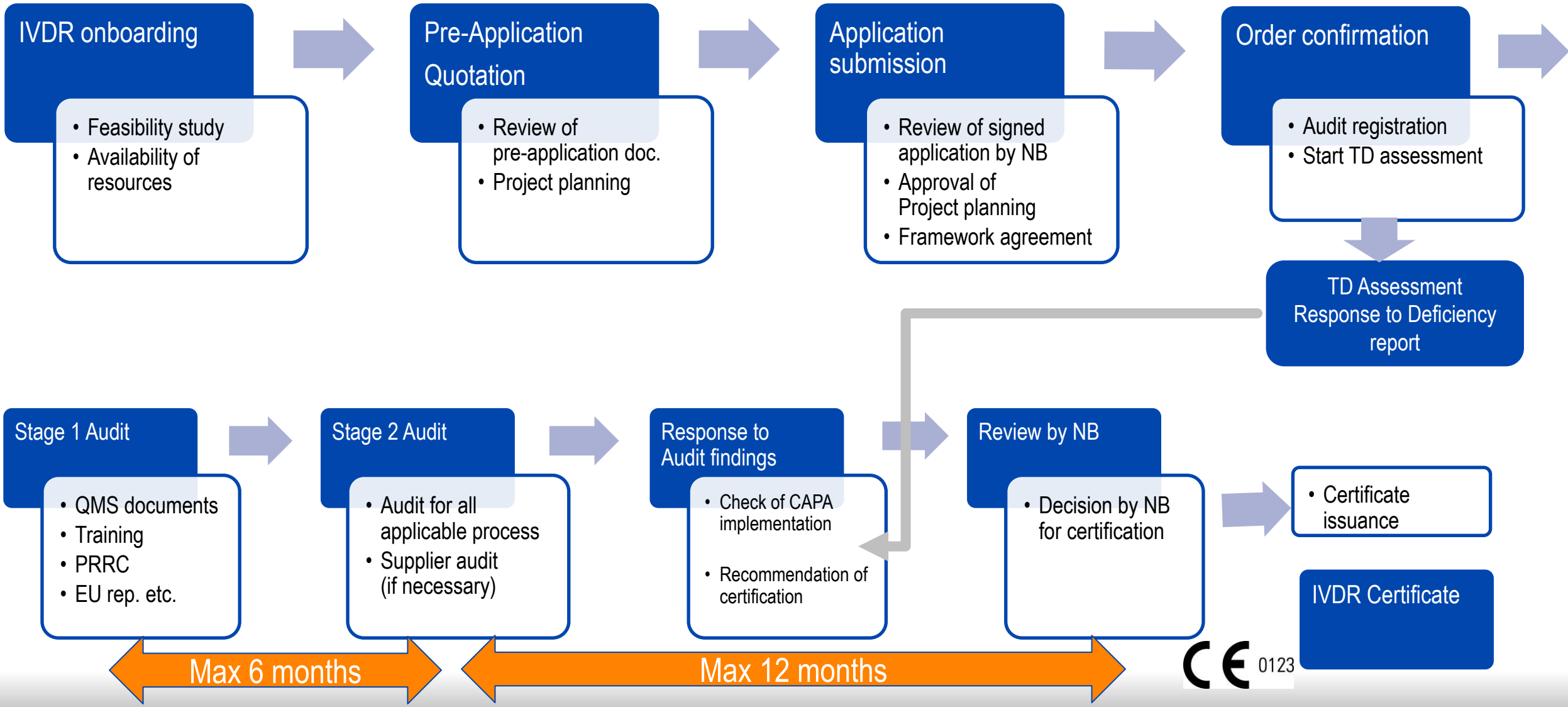
Mehr Sicherheit.
Mehr Wert.

Choose certainty.
Add value.

Agenda

- CE marking certification process
- Successful CE marking certification - example
- Key learnings from return on experience
- Question and Answers

IVDR Certification process



Successful CE marking case

Company Awesome Diagnostic have an extensive IVD portfolio

- Device List contained 7 sampling groups (3 class B, 4 class C)
  - Devices intended to be used in screening, diagnosis, staging or monitoring of cancer, or to be used to determine markers of infections/immune status, or to be used for non-infectious pathologies, physiological markers, disorders / impairments and therapeutic measures
  - Devices intended to be used to detect the presence of, or exposure to an infectious agent including sexually transmitted agents or to determine markers of infections / immune status
  - Other devices intended to be used to determine markers of infections / immune status
  - Devices intended to be used for screening, determination or monitoring of physiological markers for a specific disease
  - Devices intended to be used in screening, diagnosis, staging or monitoring of cancer, or to be used to determine markers of infections/immune status, or to be used for non-infectious pathologies, physiological markers, disorders / impairments and therapeutic measures
  - Devices intended to be used in screening, diagnosis, staging or monitoring of cancer, or to be used to determine markers of infections/immune status, or to be used for non-infectious pathologies, physiological markers, disorders / impairments and therapeutic measures
  - Devices intended to be used for screening, determination or monitoring of physiological markers

Successful CE marking case – Phases of the project

- Phase 1: Preparation to the transition
  - Review of the entire portfolio
  - Prioritization of the portfolio
  - Gap analysis of data
  - Staffing accordingly
  - Starting communication with Notified Body
- Phase 2: Submission of Pre-application documents
  - Classification of the devices / codes related to requested service were identified, correct and unambiguous
  - Correct conformity assessment procedure was chosen by client
  - Documents filled properly and complete
- Phase 3: TD review
  - Roadmap provided in advance
  - 1 pilot TD
  - identified deficiencies from 1st TD were used to update all following TDs
  - requirements were fulfilled
  - clear structure of the TD
  - all deficiencies were closed before end of stage 2 Audit
- Phase 4: QMS audit
  - Documents were properly filled in and complete
  - All requested procedures / records were available for review
  - All applicable IVDR requirements were clearly addressed

What Can I do to be successful

What Can I do to be successful

- Perform a gap assessment of each products:
  - Intended purpose
  - Clinical evidence
  - Design and manufacturing records

- Prioritize your portfolio
  - Based on sales
  - Based on complexity (sampling)
  - Based on data gap

- Engage with a Notified Body
  - Find your Notified Body (Code and assessment route)
  - Get ISO 13485 certification
  - Provide a plan for transition

Defining Quality Technical Documentation

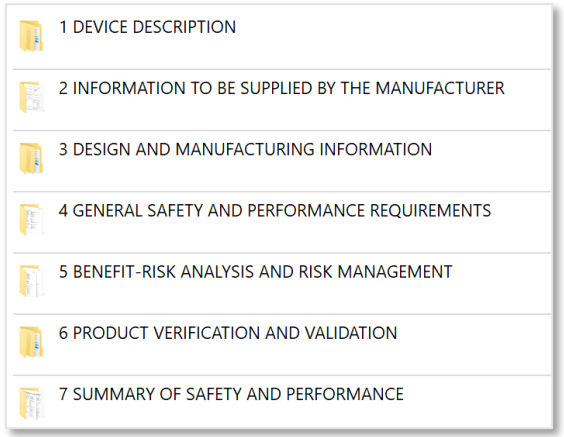
✓Organized

- Folder according to submission guidance
- **Short** and **precise** file names
- **Table of Content** including references

✓Complete

- Information according to **IVDR**
- Only **relevant** information
- **Labeling Checklist**

Wording & Consistency



✓Consistency

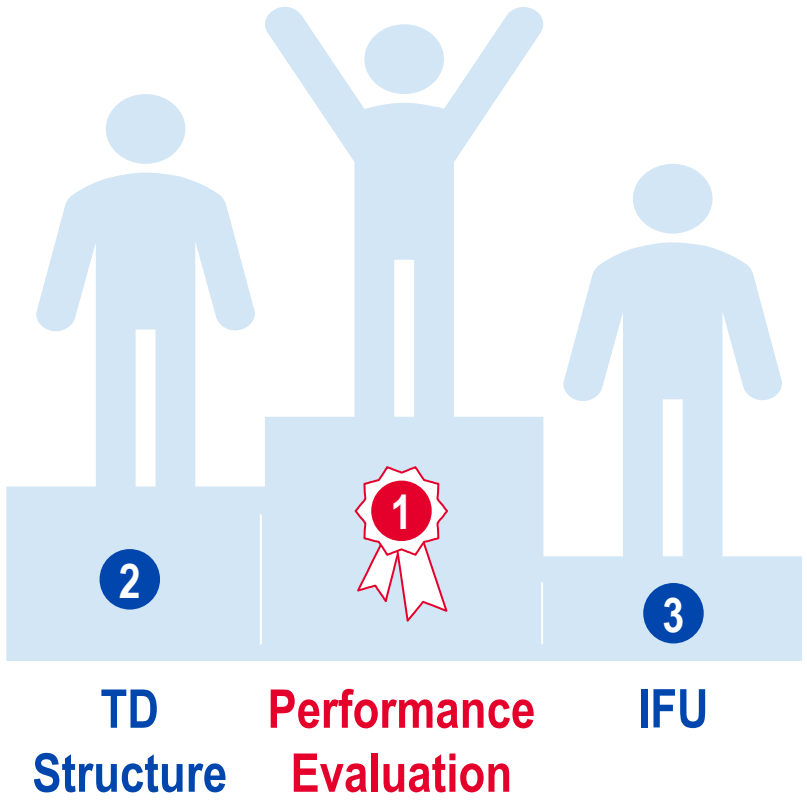
- Device name
- Catalogue no.
- Basic UDI-DI

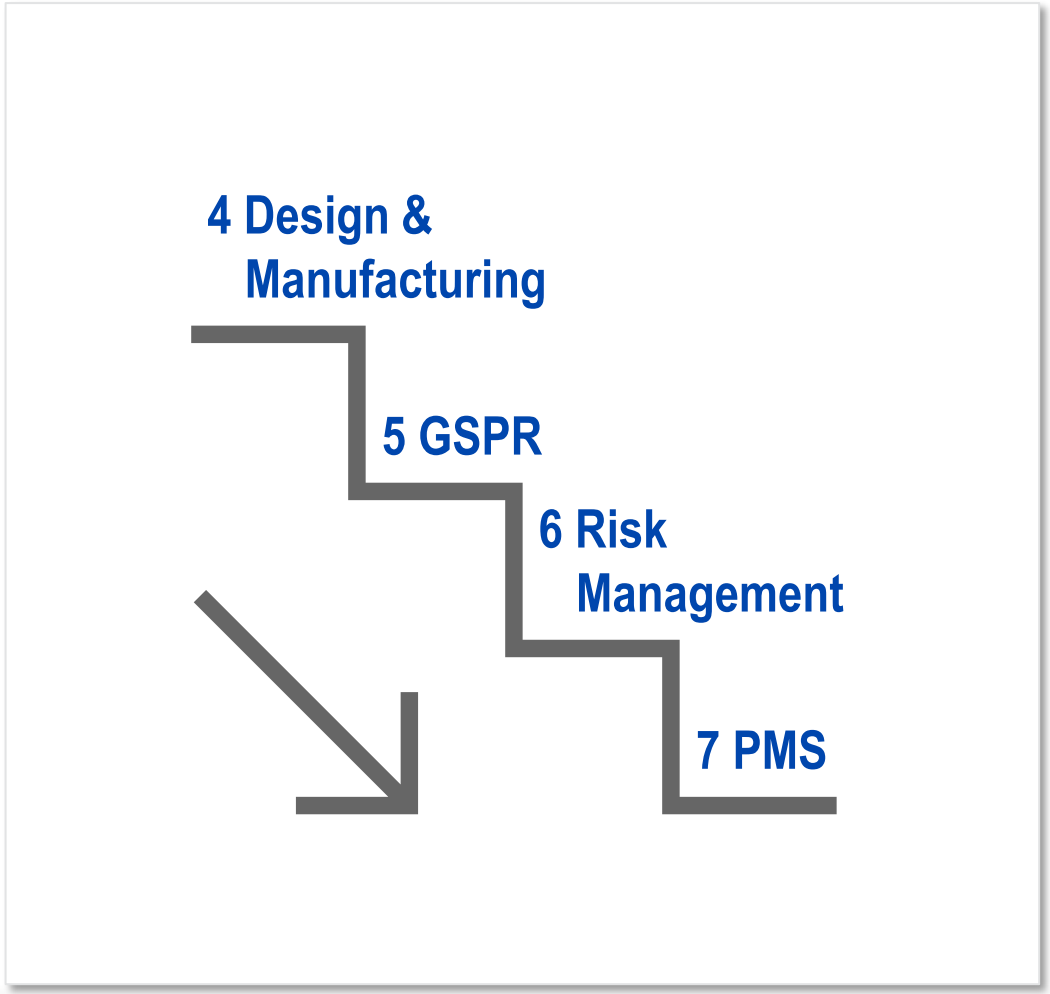
✓Searchable

- **PDF** documents
- **No scans!**

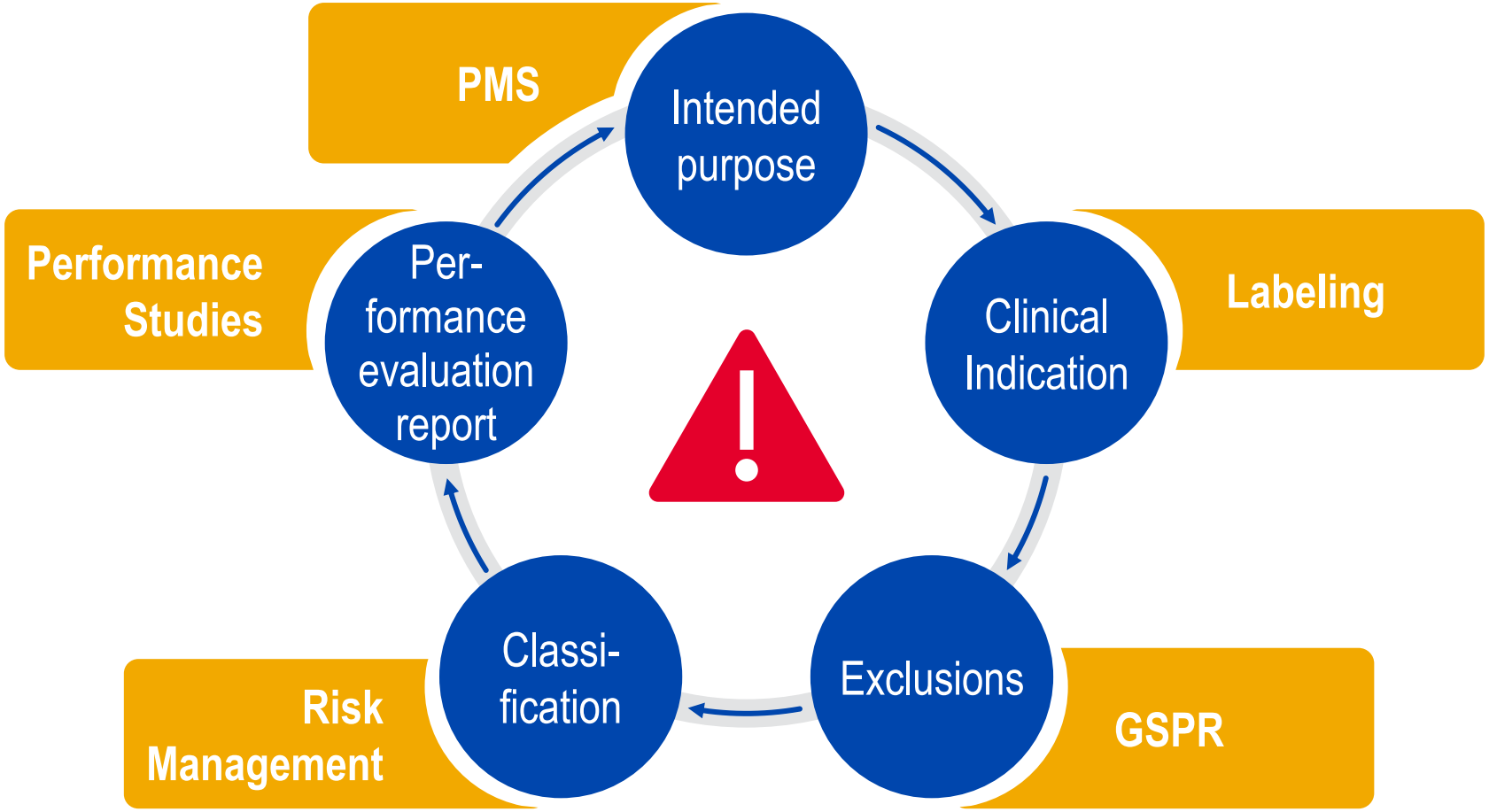
! **Relevant content of DHF and DMR needs to be translated/summarized into relevant Content for Technical File!**
No redundancies!

Major Gaps in Technical Documentation





Impact of Intended Purpose on TD assessment



Intended Purpose (IVDR Annex II 1.1 (c))

Intended purpose' means *the use for which a device is intended according to the data supplied by the manufacturer on the label, in the instructions for use or in promotional or sales materials or statements or as specified by the manufacturer in the performance evaluation*

i. *what is to be detected and/or measured* **Which analyte is to be measured?**

ii. *its function such as screening, monitoring, diagnosis or aid to diagnosis, prognosis, prediction, companion diagnostic*
For which purpose?

iii. *the specific disorder, condition or risk factor of interest that it is intended to detect, define or differentiate*
Which Indications for Use?

iv. *whether it is automated or not* **Instrument used?**

v. *whether it is* **qualitative, semi-quantitative or quantitative?**

vi. *the type of specimen(s) required*
e.g. serum, plasma, urine, cerebrospinal fluid), including any additives like anticoagulants that are required

vii. *Where applicable the* **testing population**

viii. *The intended user* **Professional User, NPT or Lay Person (ST). Intended Use setting?**

ix. *in addition, for* ***companion diagnostics****, the relevant target population and the associated medicinal product(s)*

CDx: Tradename can be included, but INN is requirement. If 2 intended purposes, which claims are not for CDx application?

Impact of Intended purpose on TD assessment

Device	Total ß Human chorionic gonadotropin (hCG)		
Intended Purpose	Pregnancy test		Tumor marker
Device Class/Rule	Class B, Rule 6	Class B, rule 4(a)	Class C, Rule 3(h)
Risk	Review every 3 years. For ST user risks very important		Annual review
Performance	According to intended purpose. Usability studies with lay users		According to intended purpose
PMS	Type of report: **PMSR** ▪ NB review during conformity assessment ▪ **Sampling approach allowed**	Type of report: **PMSR** ▪ NB review during conformity assessment ▪ **Sampling approach not allowed**	Type of report: **PSUR** ▪ NB review during conformity assessment ▪ **Sampling approach allowed**
			SSP and EudaMed

Examples Rule 3 – CMV

Device	CMV			
Intended Purpose	Screen blood and tissue donations	Detecting the presence of an infectious agent, significant risk of death or severe disability	Prenatal Screening	Infectious disease status or immune status
Device Class/Rule	Class D, Rule 1	Class C, rule 3(c)	Class C, rule 3(d)	Class C, rule 3(e)
Codes	IVR 0502	IVR 0503	IVR 0501	IVR 0504

It may be possible for a device to fall under more than one Rule 3 indent.
Where this is the case, the most appropriate indent should always be applied, based on the intended purpose of the device.
The same applies for the IVR code.

Sampling vs Product certification!

IVDR Classification rules – Annex VIII 1.Implementing Rules

Impl. Rule	Intended purpose of the device	Application of classification rules
1.6	Control materials with quantitative or qualitative assigned values, for 1 specific analyte or multiple analytes	Classification into the same class as device
1.7	Determining proper classification	All classification and implementation rules shall be considered
1.8	Multiple intended purposes → more than 1 class	Classification into the higher class
1.9	Several classification rules apply to the device	Classification rule resulting in higher classification shall apply
1.10	First line assays, confirmatory assays, and supplemental assays	Each classification rule shall apply

Basis of Conformity Assessment

Applied Standards and Evidence of Conformity

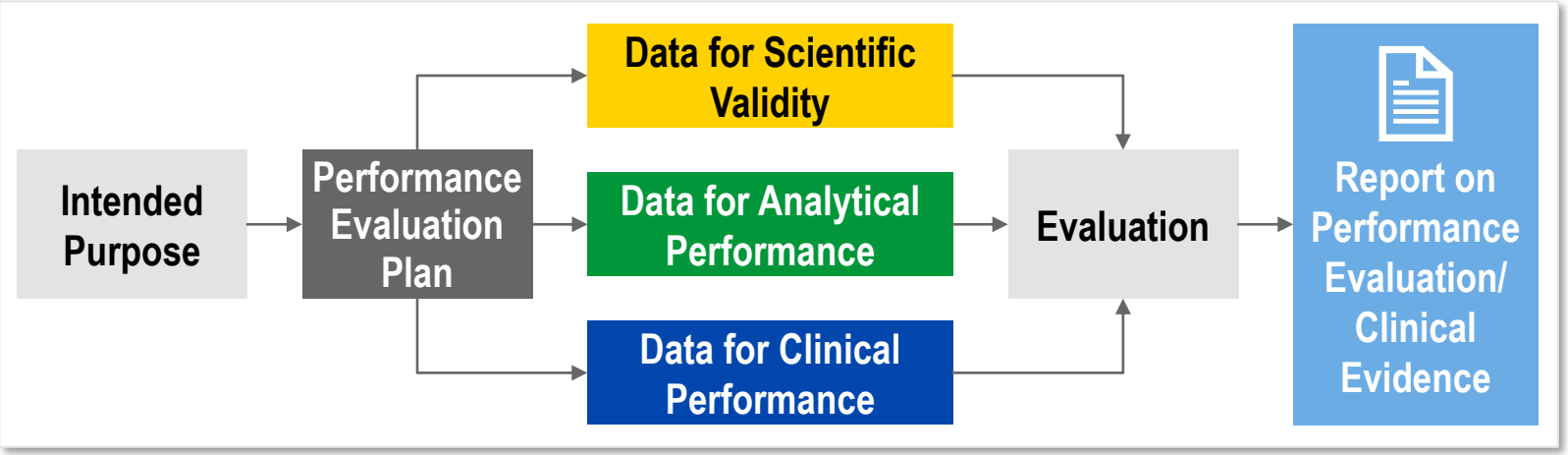
- **Unambiguous identification** of applicable device
- Evidence on **document control**
- Application of **current valid versions of standards**
- **Traceable** document evidence
- **Justification** in case of non-applicability of requirements
- **Consistency** to Technical Documentation

Gaps in GSPR Checklist

- **Justification** in case of non-applicable requirements not provided
- **Missing GAP analysis** in case former standard version has been applied
  - e.g. EN 62366:2008 vs EN 62366-1:2015/ AC:2015
- **Inconsistencies** to TD

Clinical Evidence (IVDR Article 56 /Annex XIII)

MDCG 2022-2: Guidance on general principles of clinical evidence for Invitro Diagnostic Medical Devices (IVDs)



Gap Analysis for Legacy Devices

Individual patient risks need to be considered
→ **Generic approaches** according to risk class not sufficient

- **Clinical Benefit**
- **Device Safety**
- **State-of-the Art**

- Clinical Evidence is a continuous Process following the **PEP**
- Coordination of **risk management with performance evaluation**
- Regular update - **post-market data** (PMS, PMPF)
- **Scientific Validity** can be abbreviated in case of very established markers (e.g. blood groups)
- Conduct clinical studies unless it is duly justified to rely on other sources (literature, routine diagnostic)
- Include always justification in reports

General Gaps on Performance Studies

- Individual **Plans** (PEP, CPP)
- Individual **Reports** (APR, SVR, CPR)
- Summary **Study Reports**
- Conclusion on **Clinical Evidence** in PER

- **Report Format** not compliant to IVDR
- **No Gap Analysis** for Legacy Devices!
- **Rationale missing** in case of non-applicable performance parameters
- **Insufficient Study details** including acceptance criteria, applied statistical methods
- **Result presentation** not sufficient (Passed/Fail)
- **Conclusion** of study outcome not presented
- **Explanation** of specific terms/methods and Abbreviations is missing

Annex IX 4.5 – In case, clinical evidence of device in question is based partly or totally on data from **previous generation of devices** which are claimed to be equivalent to the device under assessment, **relevant and adequate data for demonstration of conformity are required**.

Gaps in Analytical Performance

State-of-the Art	**Similar devices** for state-of-the-art comparison are not used for method comparison, not described or not included at all **(recommendation EXPERT Panel)**
Specimen	**Origin of samples** (spiked vs clinical)? Specimen stability: temperature and time period?
Accuracy	Availability of standards, international reference methods? → Method comparison!
Analytical Sens	Results with **Standard**? (CTS/CS)
Interferences	**Relevant specimens** not tested, **Disease-specific drugs** not tested
Cross-reactivity	Needs to be tested for screening and confirmatory assay (CTS/CS)
Cut-off	**Cut-off** and **calculation of data**?
RT-Stability	Only Accelerated Stability Data provided
In-use stability	Data not provided or not mentioned in IFU
Transp. stability	Data not provided or no product-specific performance studies (e.g. only Drop test)

Gaps in Clinical Performance

Clinical Performance Studies

- **Origin of Samples** unclear:
  Sample acquisition? European?
- **Study sites?**
- **Gap analysis** for old data (previous generation)?
- **Similar device** not used/described
- **Cut-off** and **calculation of data**?
- **Conclusion**?

Scientific Peer-rev. Literature

- Report completely **missing**
- Only **old** references or **textbooks**
- **Literature references?**
- **Search Protocol?**
  - Sources, Inclusion/Exclusion criteria?
- **Similar gaps in SVR** with regard to Literature approach

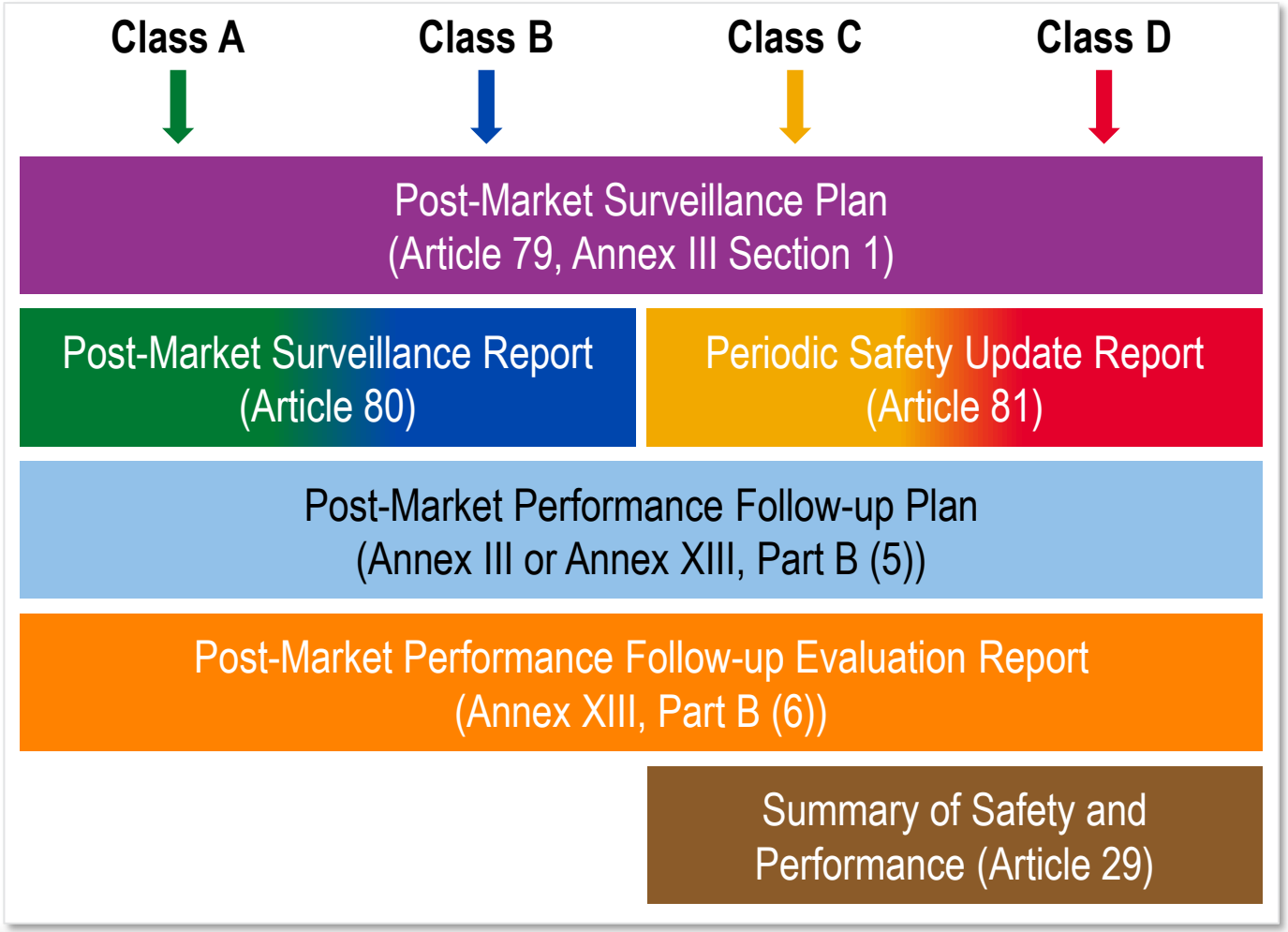
Clinical performance report

Correlation is detected and documented, the product provides results that correspond to a particular clinical condition or physiological or pathological process or condition, a specific target population and certain intended users
Studies can be omitted in exceptional cases, but justification required!

Gaps in Design and Manufacturing (IVDR Art 10.1, Annex II 3, 6.5)

- Information on **Design and Development is missing**
- Information on Manufacturing Process not sufficient
  - **Flowchart** with IC, IPC and outsourced processes
- Identification of all sites including suppliers and sub-contractors
  - Definition of **critical ingredients vs critical supplier!**
- ***Annex II 6.5b*** *In the case of devices containing tissues, cells and substances of animal, human or microbial origin, information on the origin …*
  - Specifications and Control measures **(CoA, MS) are missing**

Post-Market Surveillance /Post-market Performance Follow-up



- First **Assessment on Surveillance activities** according to Annex III (PMS Plan, PMPF Plan/report (PMSR/PSUR) just started
- For **initial certification** only PMS and PMPF Plan required
  - Not all IVDR requirements fulfilled in some cases
  - If PMPF is not performed, rationale missing or not provided in PER
- **SSP: MDCG 2022-9 (SSP Template)**
  - For certification final SSP required for future EUDAMED upload
  - Some information not provided or cross reference to IFU is not correct

Claims in Labeling – IFU (IVDR Annex II 2, Annex I 20)

Most important gaps observed in IFU (Annex I, Chapter III, 20.4)

(b) the details strictly necessary for the user to uniquely identify the device ***(inconsistencies)***

(c) the device's intended purpose **(not all elements defined, wording not specific enough)**

(e) *the intended user* **(not defined)**

(i) a list of materials provided and a list of special materials required but not provided **(not clear)**

(l) in-use stability **(missing)**

(q) conditions for collection, handling, and preparation of the specimen **(specimen stability)**

(w) analytical performance characteristics **(gaps in claims)**

(x) clinical performance characteristics **(gaps in claims)**

(ae) date of issue of the instructions for use **(version history is missing)**

- Consistency between Claims and Technical Documentation
- All variants covered? Traceability?
- Translations of Labelling prior to IVDR launch

Key Takeaways

- Submission of **complete and quality** Technical Documentation
- **All elements of Intended Purpose** need to be clearly defined
- **Gap Analysis** is required in case of **Legacy Devices**
- Demonstration of **State-of-the Art Performance**
- Check on **Consistency between Claims in Labeling and Technical Documentation**

Consistency is Key!

? QUESTIONS ?

спасибо
GRACIAS 谢谢
THANK YOU
ありがとうございました MERCI
DANKE धन्यवाद
شُكراً OBRIGADO
Gracie
감사합니다

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