IVDR Workshop
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Genau. Richtig.

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Agenda

Kapitel	Thema
1	IVD Directive
2	Overview (incl. transition period, general aspects)
3	Classification
4	Conformity Assessment
5	General Safety und Performance Requirements / Technical Documentation
6	Clinical Evidence
7	Performance Evaluation
8	Post-Market Surveillance
9	Notified Body related aspects

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IVD Directive 98/79/EC

Classification according to IVDD 98/79/EC

- **List A:** high risk IVDs
- **List B:** moderate risk
- IVDs for **self-testing** (lay users)
- "**other IVDs**"

List A:

- *Virology*
- HIV 1 and 2
- HTLV I and II
- hepatitis B,C,D
- vCJK disease (new)

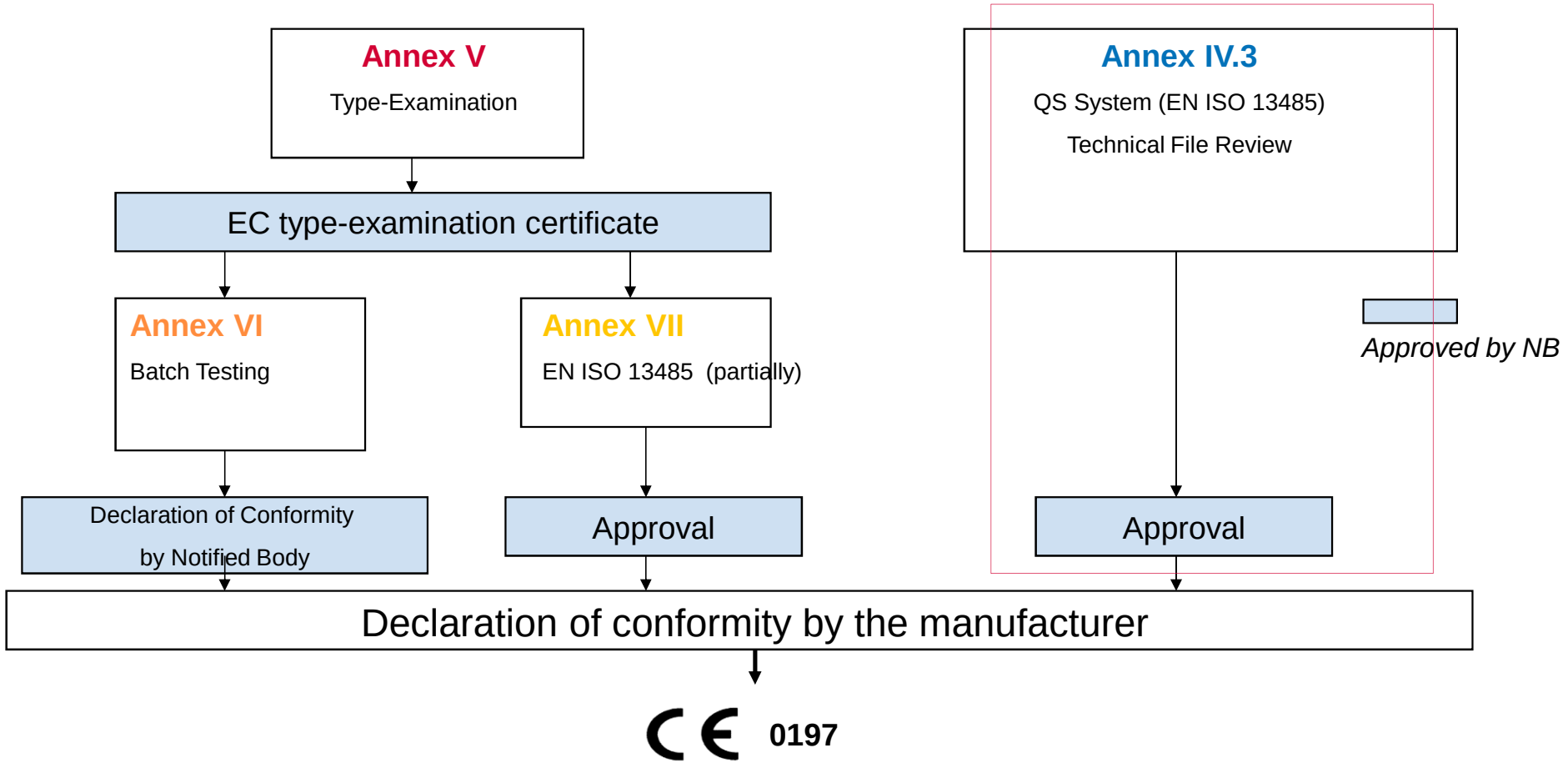
- *Blood Groups*
- AB0 system
- rhesus (C,c ,D ,E ,e)
- anti-Kell

List B:

- anti-Duffy, anti-Kidd
- irregular anti-erythrocytic antibody

- rubella, toxoplasmosis
- phenylketonuria
- cytomegalovirus, chlamydia
- HLA tissue groups: DR, A, B
- tumoral marker: PSA
- evaluating the risk of trisomy 21
- device for self-diagnosis: measurement of blood sugar

IVD Directive 98/79/EC - Conformity Assessment – Annex II List B



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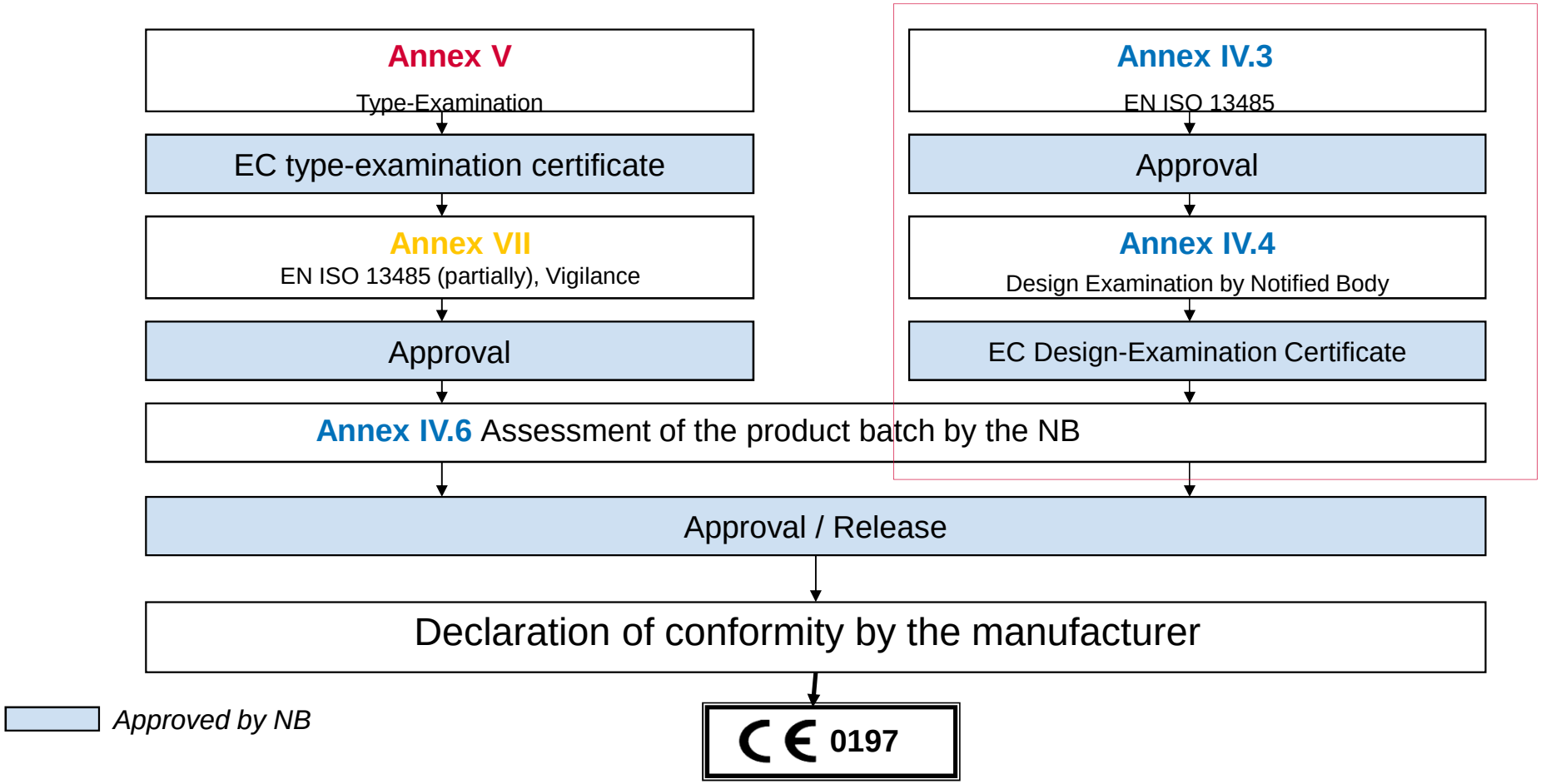
IVD Directive 98/79/EC - Conformity Assessment – Annex II List A



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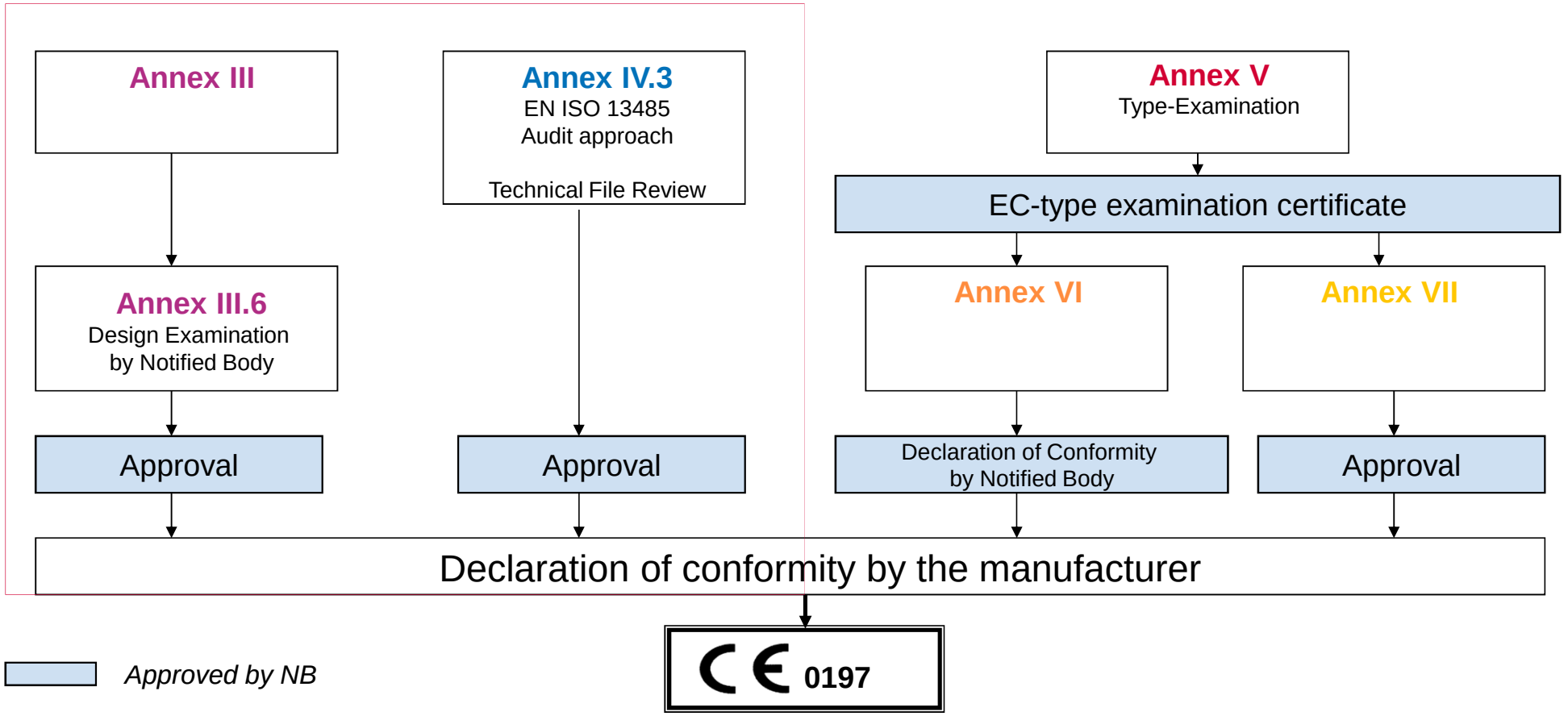
IVD Directive 98/79/EC - Conformity Assessment – self-testing devices



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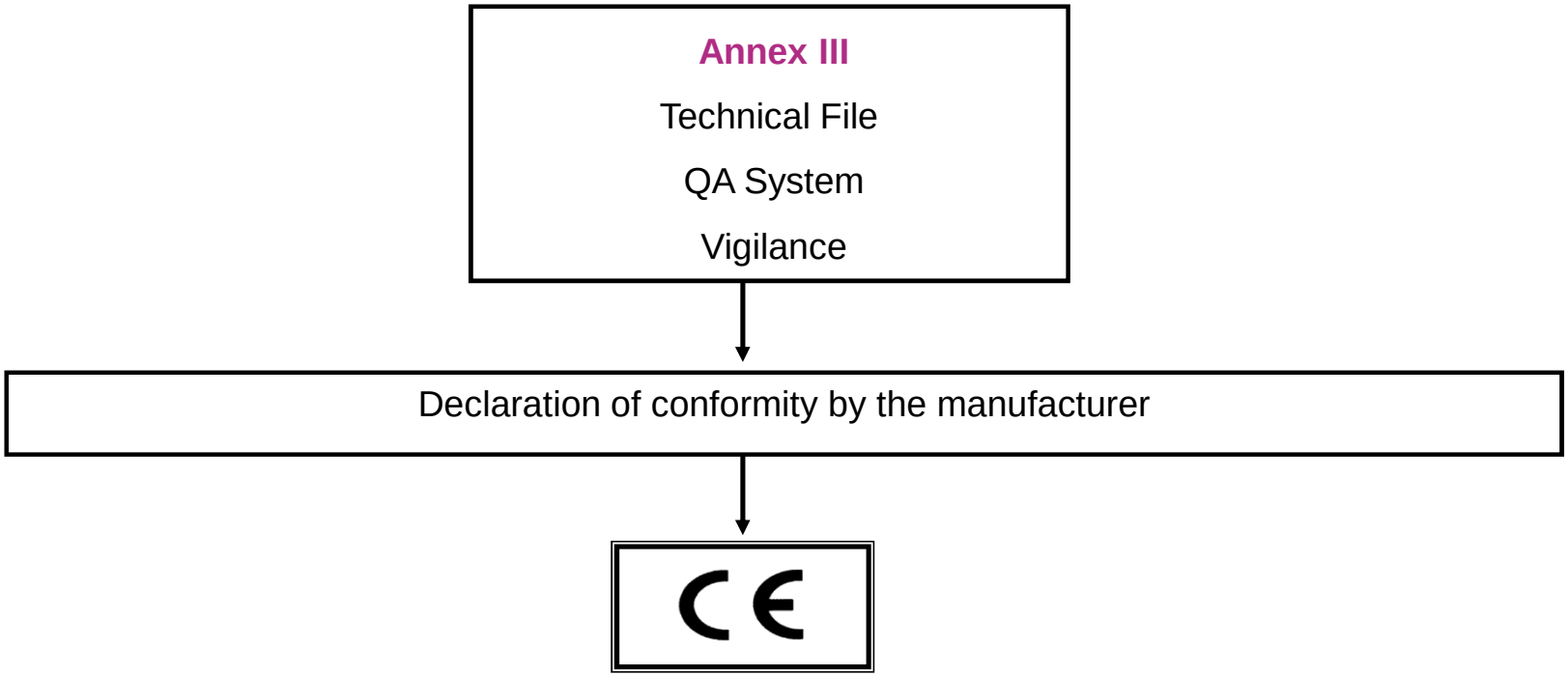
IVD Directive 98/79/EC - Conformity Assessment – “other IVDs”



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Introduction – regulatory landscape

Directive 98/79/EC –
in vitro diagnostic medical devices

In **V**itro **D**iagnostic **R**egulation
(IVDR)
2017/746

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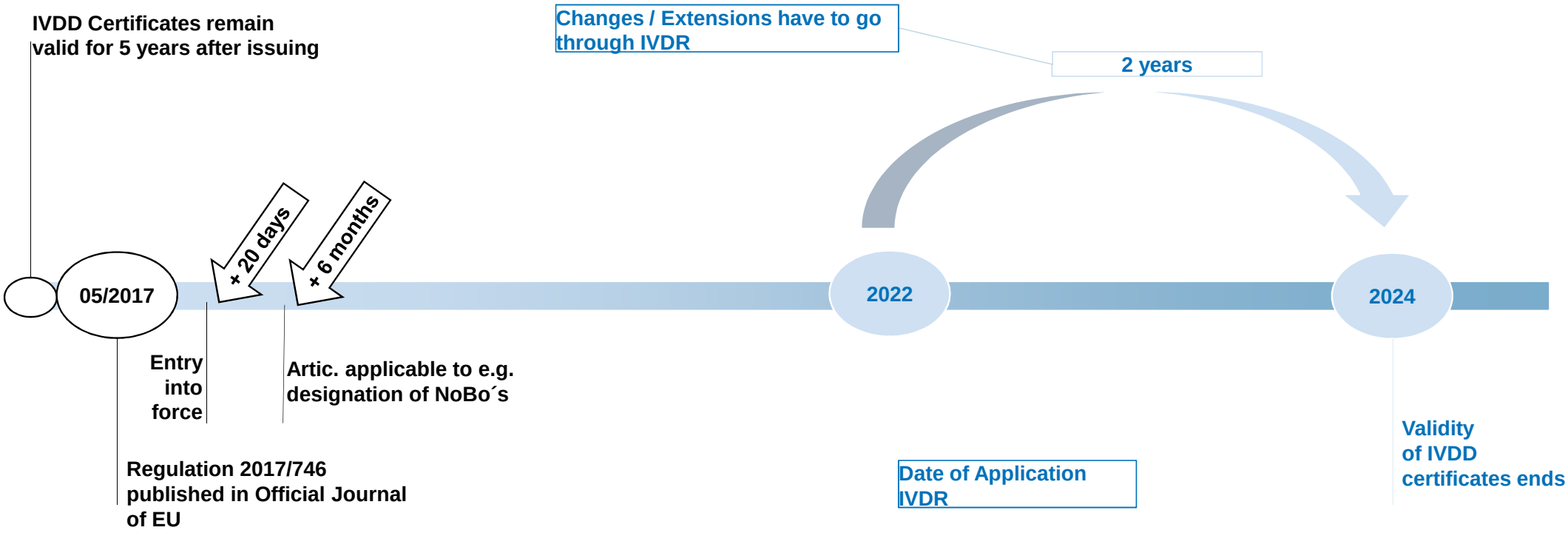
Overview - Transition Period

Transition Times



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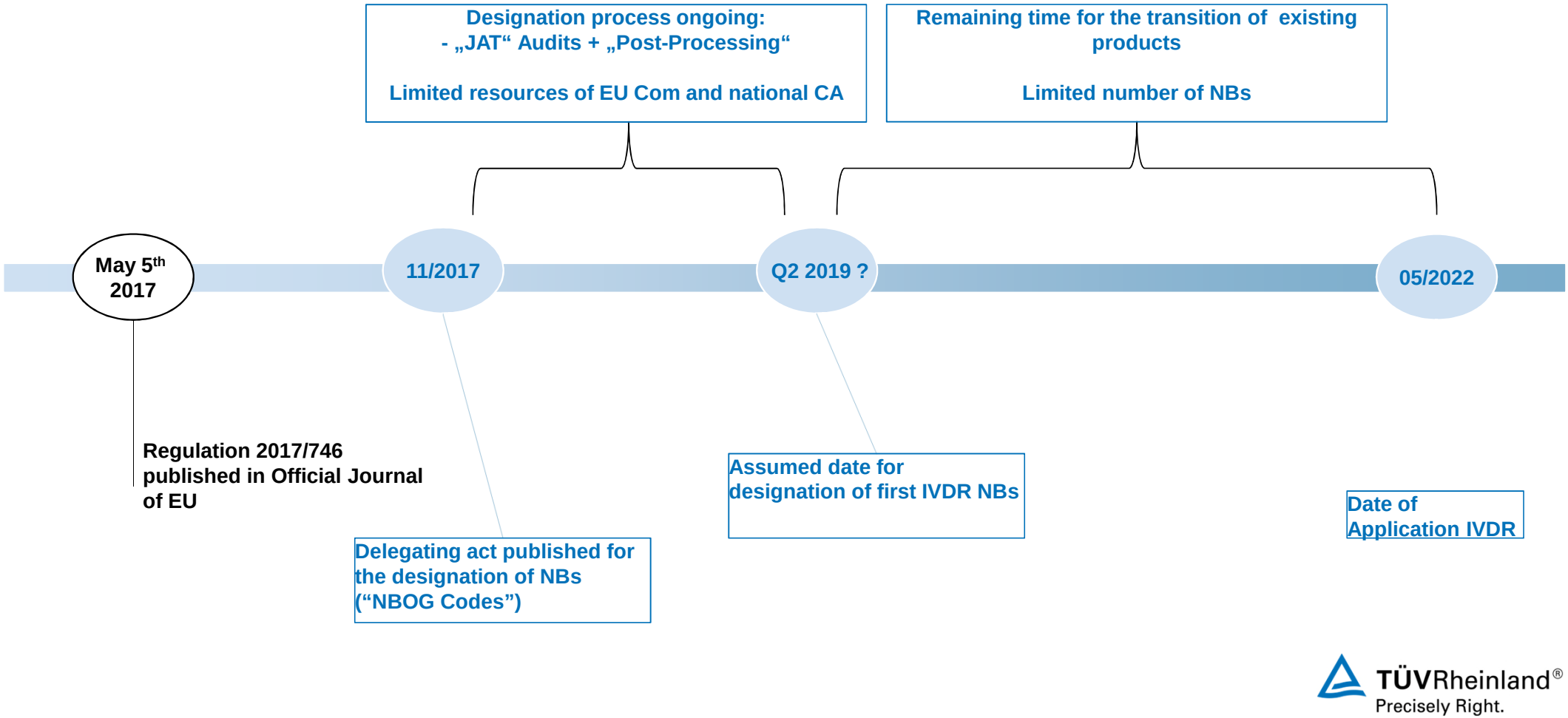
Overview – Designation of Notified Bodies (NBs)

Transition Times



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Overview

Transitional provisions

- Devices placed on the market according to IVDD prior to 26th May 2022 may continue to be made available on the market or put into service until 27th May 2025
- EU Reference Laboratories start working after 25th November 2020
- UDI applies from:
  - May 26th 2023 for class D devices
  - May 26th 2025 for class B and C devices
  - May 26th 2027 for class A devices

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Overview

Implementation status

CAMD IVDR Roadmap

NEWS_171107_MDR-IVDR_RoadMap_v1.3-1.pdf

IVDR Rolling implementation plan

https://ec.europa.eu/docsroom/documents/31902

MDR / IVDR Corrigendum planned (Q1 2019?)

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Introduction

Structure - Chapters (Articles)

Chapter I Scope and definitions

Chapter II Making available and putting into service of devices, obligations of economic operators, reprocessing, CE marking, free movement

Chapter III Identification and traceability of devices, registration of devices and of economic operators, summary of safety and clinical performance, European databank on medical devices

Chapter IV Notified Bodies

Chapter V Classification and conformity assessment

Chapter VI Clinical evidence, performance evaluation and performance studies

Chapter VII Post-market surveillance, vigilance and market surveillance

Chapter VIII Cooperation between Member States, Medical Device Coordination Group, EU **reference laboratories**, device registers

Chapter IX Confidentiality, data protection, funding, penalties

Chapter X Final provisions

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Introduction

Structure – Annexes

Annex I General Safety and Performance Requirements

Annex II Technical Documentation

Annex III Technical Documentation on Post-Market Surveillance

Annex IV EU Declaration of Conformity

Annex V CE Marking of Conformity

Annex VI Registration / UDI

Annex VII Requirement to be met by Notified Bodies

Annex VIII Classification Criteria

Annex IX Conformity Assessment (QMS)

Annex X Conformity Assessment (TYPE EXAMINATION)

Annex XI Conformity Assessment (PRODUCTION QUALITY ASSURANCE)

Annex XII Certificates issued by a NB

Annex XIII Performance Evaluation. Per. Studies and Post-Market Perf. Follow up

Annex XIV Interventional clinical performance studies

Annex XV Correlation Table

Recitals: 101
Definitions: 74
Articles: 113
Annexes: 15
Pages:
157 IVDR vs 47 IVDD

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Overview

Definitions (Chapter I / Article 2)

'in vitro diagnostic medical device' means any medical device which is a reagent, reagent product, calibrator, control material, kit, instrument, apparatus, equipment, **software or system**,……., solely or principally for the purpose of providing information:

- concerning a physiological or pathological process or state
- concerning congenital physical or mental impairments
- concerning the **predisposition** to a medical condition or a disease (e.g. genetic test)
- to determine the safety and compatibility with potential recipients
- to **predict treatment response or reactions** (Companion Diagnostics (CDx))
- to define or monitor therapeutic measures

Overview

Scope - Chapter I / Article 1

IVDR does <u>not</u> apply to:

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

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Overview

Definitions (Chapter I / Article 2)

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

- identify…..patients who are most likely to benefit from the corresponding medicinal product; or

- identify….patients likely to be at increased risk for serious adverse reactions as a result of treatment with the corresponding medicinal product;

'device for near-patient testing' means any device that is not intended for self-testing but is intended to perform testing outside a laboratory environment, generally near to, or at the side of, the patient by a health professional;

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Legal Manufacturer – OEM/PLM (Article 1 / Article 10)

Definition manufacturer:

(23) ‘manufacturer’ means a natural or legal person who manufactures or fully refurbishes a device **or has a device designed, manufactured** or fully refurbished, **and markets that device under its name** or trade mark;

„PLMs“:

Full responsibilities of a LM
Full TD to be maintained
No PLM „chains“ allowed

Obligations of manufacturers:

….

4. Manufacturers **shall draw up and keep up to date the technical documentation for** 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.

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Overview

In-house products (Article 5.5)

General safety and performance requirements set out in Annex I are applicable as well

However **no conformity assessment**

Defined **prerequisites**, e.g.:

- devices manufactured and used only within health institutions
- the device is not transferred to another legal entity
- Does not apply to products manufactured on an industrial scale
- manufacture and use of the device occur under appropriate quality management systems
- **the health institution justifies in its documentation that the target patient group's specific needs cannot be met or cannot be met at the appropriate level of performance by an equivalent device available on the market**

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Overview

Economic operators

Extended responsibilities of **distributors and importers** („**Economic operators**“) involved in the supply chain, (Art. 10/ 11/12/ 13/ and 14 defines the general obligations of each part).

- Full traceability in both directions (Art. 25)
- Obligation to cooperate in case of enquiries by Competent Authorities or requests for recall / withdraw (Art. 13/ Art. 72/ Art. 95)
- Each economic operator **can be subject to an unannounced audit** by the Notified Body (Contractual agreements between legal manufacturer and EO!)

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Overview

Economic operators

Obligations of **importers** (Article 13), e.g.:

- **Conformity** of the imported product (Duty to verify CE mark + DoC, correct labelling (UDI + LM + EC rep) and existance of IFU)
- Verification of registration in EUDAMED
- Obligation to record complaints, non-conforming products and recalls and to inform the legal manufacturer / authorized rep.
- Obligation to inform the LM / EC rep and (in case of risk) Competent Authorities and NB if device does not conform
- **Importer to be indicated on the device or packaging or accompanying documen**

Obligations of **distributors** (Article 14), e.g.:

- Duty to verify CE mark, correct labelling (UDI) and existance of IFU (indication of im **acceptable except for indication of importer**
- Obligation to record complaints, non-conforming products and recalls and to inform t authorized rep. / importer
- Provision of free-of-charge product samples to CA upon request

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Overview

Article 11 - Authorised representative

Examples of obligations:

- **verify** that the EU declaration of conformity and technical documentation have been drawn up and, where applicable, **that an appropriate conformity assessment procedure has been carried out** by the manufacturer
- **keep available a copy of the technical documentation**, the EU declaration of conformity and, if applicable, a copy of the relevant certificate
- comply with the **registration obligations** and verify that the manufacturer has complied with the registration obligations
- in response to a **request from a competent authority**, provide that competent authority with all the information and documentation necessary to demonstrate the conformity of a device, in an **official Union language** determined by the Member State concerned
- ……, the authorised representative shall be **legally liable** for defective devices on the same basis as the manufacturer.

Overview

Article 15 - Person responsible for regulatory compliance

Manufacturers shall have **available within** their organisation, **at least one person** responsible fo
compliance who possesses the requisite expertise….

- University degree in a relevant scientific discipline + 1 year professional experience in RA or
- or 4 years professional experience in RA or QMS for IVDs

Exemption for micro and small companies

Responsible to ensure:

- **Conformity of the device** in accordance with the **quality management system**
- **Technical Documentation** and the declaration of conformity are drawn up and kept up-to-date
- **Post-market surveillance** obligations fulfilled
- **Reporting obligations** as part of the **vigilance** system

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Classification

IVD Directive	IVD Regulation
List A: *high risk IVDs* *(e.g. blood donor screening, HIV,HCV)* ***List B:*** *moderate risk IVDs* *(e.g. prenatal markers, infectious diseases)* ***IVDs*** *for self-testing* *(lay users)* ***"other IVDs"***	**Annex VII** **Rule based classification system (7 rules)** Origin GHTF model 4 risk classes: **A, B, C and D**

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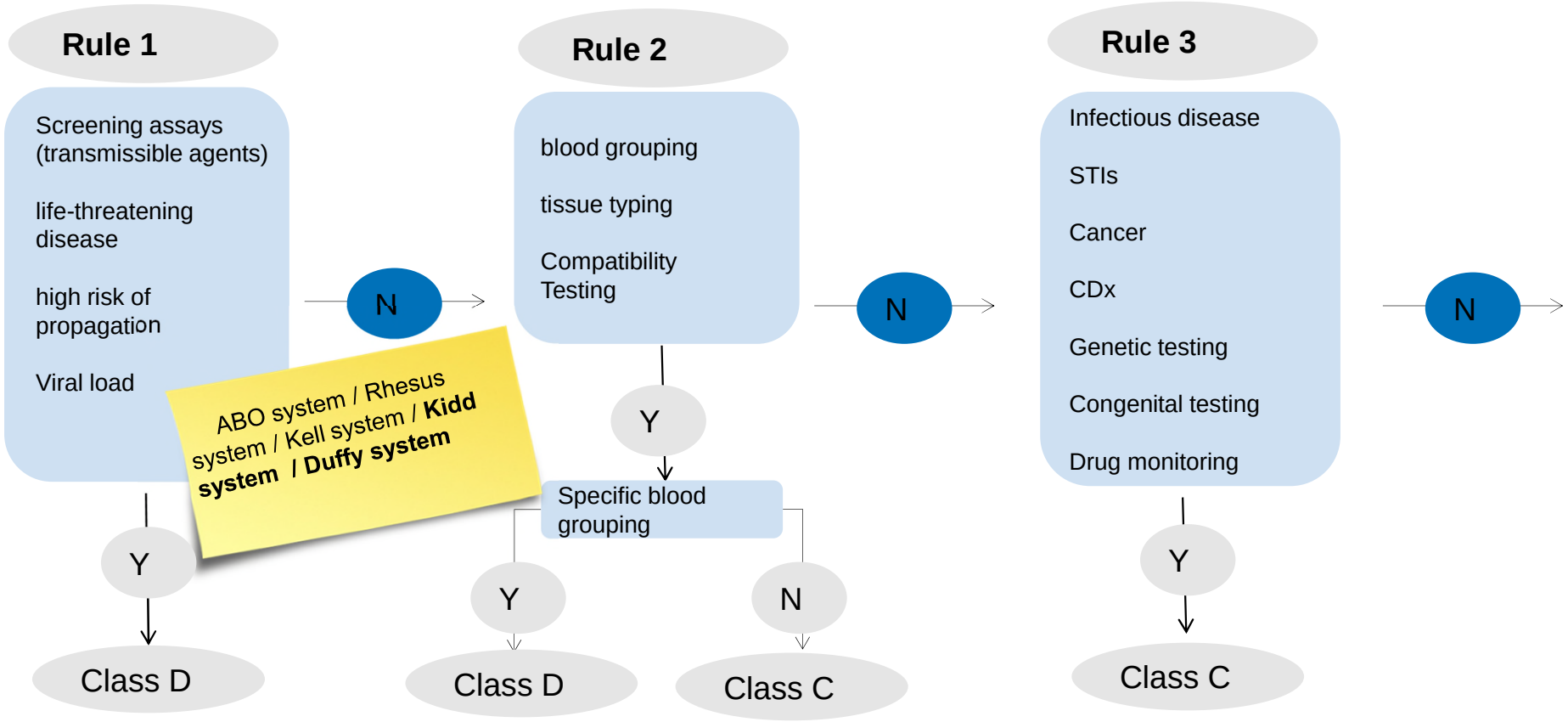
Classification



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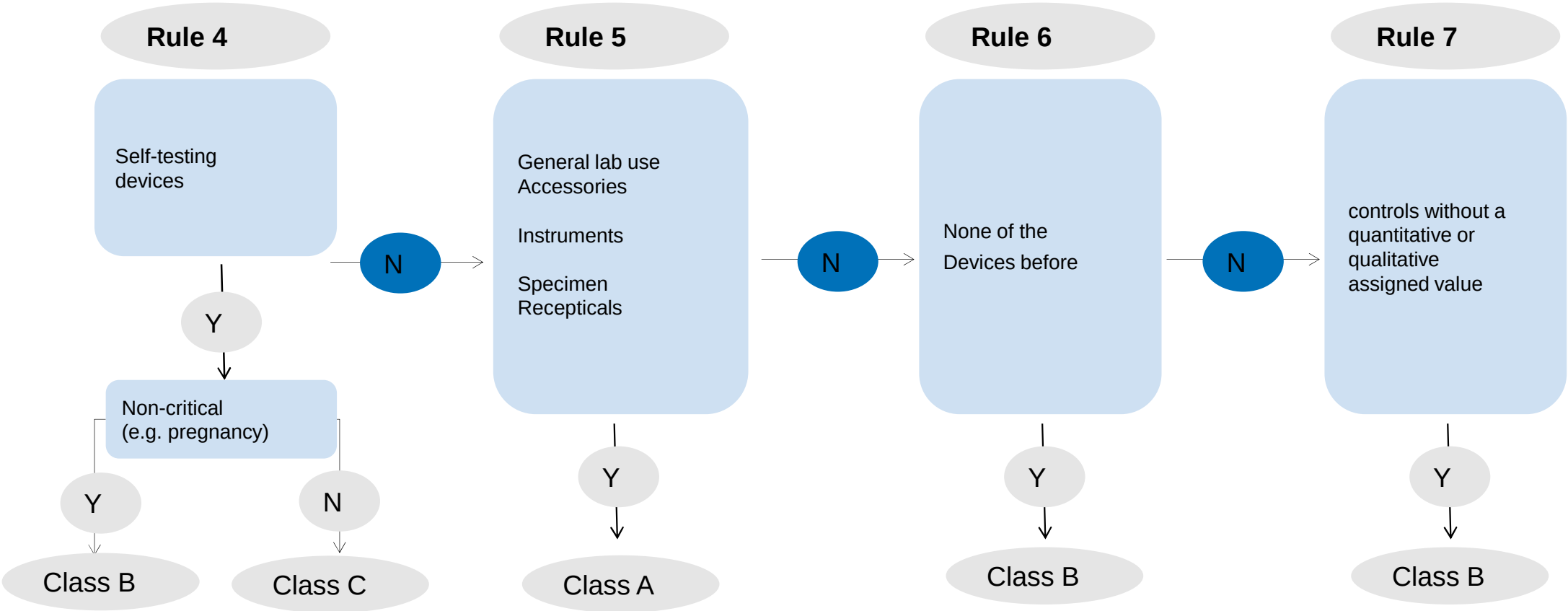
Classification



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Classification

Impact of new classification

2017

“Self-declared” IVDs

IVD products
NoBo obligatory

2022

“Self-declared” IVDs

IVD products
NoBo obligatory

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Classification

Class	Risk	Examples
A	Low individual risk and low risk to public health	Analyzer for clinical chemistry, sample containers
B	Moderate individual risk and/or low risk to public health	Vitamine B12, pregnancy self-tests, urine test strips
C	High individual risk and/or medium risk for public health	Blood glucose self-tests, HLA typing, PSA tests, Rubella, cancer diagnostics, CDx
D	High individual risk and high risk for public health	Blood donor screening (HIV/HCV), blood grouping (A,B,O)

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Classification

“Markers“ currently discussed being class D devices

- **Blood grouping** (ABO, Rhesus, Kell, Kidd, Duffy) based on rule 2
- **Infectious agents** based on rule 1 :
  - Blood Donation Screening: HIV, Hep B/C, HTLV I/II
  - Pandemic agents: Influenza virus, SARS
  - Transplantation: CMV , EBV
  - Bacterias: Treponema pallidum , Neisseria meningitidis
  - Parasites: Malaria , Trypanosoma cruzi, Toxoplasma gondii
  - „BSL4 pathogens“: Ebola, Marburg, Lassa, Smallpox

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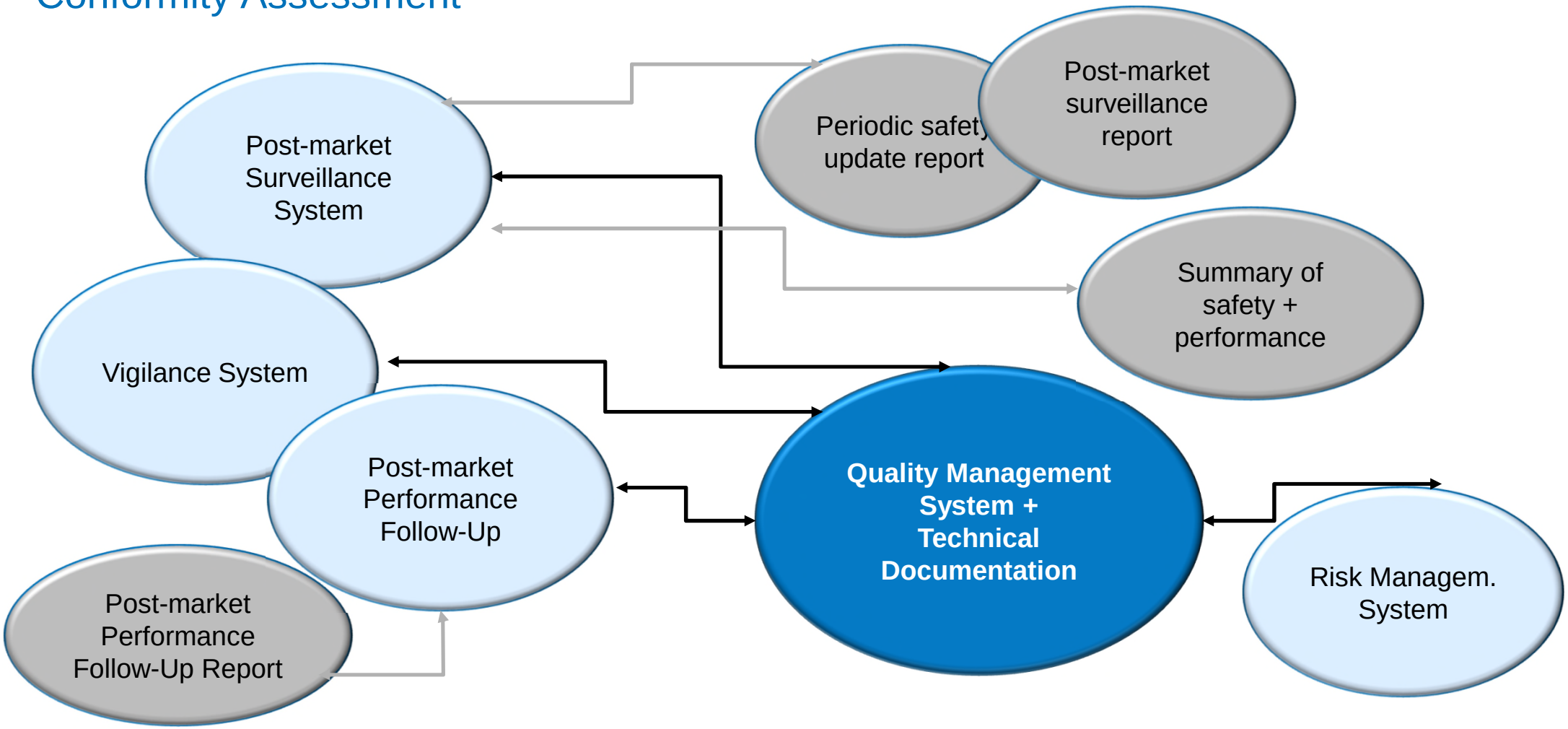
Conformity Assessment



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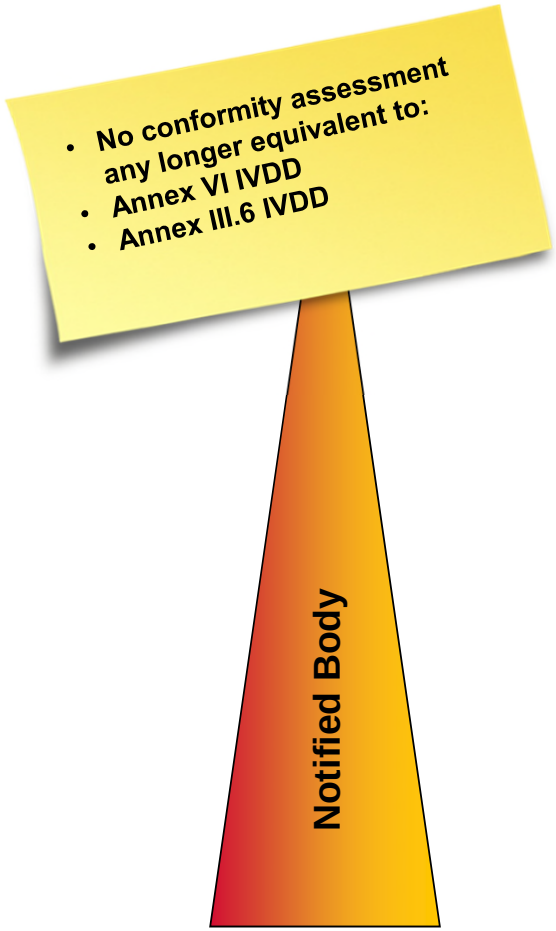
Conformity Assessment Procedures under IVDR

Class A	**Self declaration (Annex II)** **(except for sterile devices)**	
Class B	**QMS + Review of the Technical Documentation** ***Annex IX***	
Class C	**QMS + Review of the Technical Documentation** ***Annex IX***	**Type Examination** ***Annex X +*** **QMS production** ***Annex XI***
Class D	**QMS + Technical Documentation + Batch release** ***Annex IX***	**Type Examination** ***Annex X +*** **QMS production** ***Annex XI+*** **Batch release** ***Annex IX***



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Conformity Assessment – Class B + C (Annex IX)

QMS assessment - Application

Submitted for NoBo review e.g.:

- Information on device groups
- QMS documentation / procedures
- Change control procedures
- PMS procedures / plans
- Performance evaluation plan / PMPF Plan

QMS documentation to be reviewed,e.g.:

- Organisational structures / Control of outsourced processes
- Design control process / regulatory compliance processes (CS, performance evaluation, risk management etc.)
- Change control system
- QC procedures

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Conformity Assessment – Class B + C (Annex IX)

QMS – on-site audits

Based on EN ISO 13485

Audit team to be experienced with **„technology concerned“ / devices (class C)**

a **lead auditor** shall not lead [and attend] an audit for more than three consecutive years

NB may carry out or ask for **product testing**

Surveillance Audits at least once every 12 months

Audit focus:

- design and development
- production and process controls
- product documentation
- purchasing
- corrective and preventive actions including for **post-market surveillance**
- **PMPF**

- Audit of outsourced processes / suppliers if necessary

NoBo issues **audit report**

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Conformity Assessment – Class B + C (Annex IX)

Unannounced audits

randomly, at **least every 5 years**
„..may be combined with surveillance assessment..“

NoBo **shall** test **product sample** (drawn from warehouse and market)

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Conformity Assessment – Class B + C (Annex IX)

Tech. Documentation Review Class B / C

All evidences according to Annex II and III to be submitted

Review focus:

- **Clinical Evidence** as documented in the **performance evaluation report**
- benefit-risk determination, the risk management
- the instructions for use
- manufacturer's **post-market surveillance plan**, and include a review of the need for, and the adequacy of, the **PMPF**

NB reviewer:

- sufficient clinical expertise
- including **external clinical experts** with experience relating to the **clinical application** of the device

NB has to establish a sampling plan.

For class B based on „product categories“

For class C based on „generic device groups“

NoBo issues TD assessment **report**

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Conformity Assessment – Specific requirements for self-testing and POCT

Section 5.1 Annex IX- Specific requirements for self-testing and POCT

TD Assessment, applicable to class B,C and D

Focus: design and performance including:

- test reports, including results of studies carried out with intended users;
- where practicable **provision of a sample** of the device
- data showing the **suitability of the device** in view of its **intended purpose for self-testing or near patient-testing**;
- the information to be provided with the device on its label and its instructions for use.

NoBo issues **EU technical documentation assessment certificate**

As for CDx and class D devices

No sampling (?)

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Conformity Assessment – Class D (Annex IX)

QMS assessment - Application

QMS – on-site audits

Unannounced audits

Basically as stated before

Tech. Documentation Review – Class D

- assessment of TD by NoBo for the device concerned, incl:
- Design + manufacturing information
- Clinical evidence / performance
- Risk benefit

No sampling approach, however difference to TD review for class B and C to be clarified

NoBo issues TD assessment report **and certificate**

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Conformity Assessment – Class D (Annex IX)

Batch release

- **QC reports** provided to NoBo
- **Batch release testing** by reference laboratory
- Timeline: **30d** after reception of samples

Verification by reference lab

- Designated reference laboratory:
- Verification of claimed performance
- Compliance with CS
- Laboratory tests mandatory, focusing on:
- analytical sensitivity
- diagnostic sensitivity

Timeline: 60d

NoBo shall give „due consideration“

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Conformity Assessment – Class D (Annex IX)

Scrutiny

Pre-market consultation proc.

Prerequisite:
- no common specification exist + first certification for that type of device

Consultation of expert panel:
- Provision of performance evaluation report of the manufacturer

Opinion provided to NoBo within **60d** timeline

Post-market scrutiny

For **all** class D devices:
Notification of CA about newly issued certificates via EUDAMED by NoBo, accompanied by e.g.:
- Summary of safety and performance
- Assessment report of NoBo
- Test results/ scientific opinion of ref.lab
- If applicable: opinion of expert panel

CA and Commission may request actions
Commission / MDCG may request scientific advise

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General Safety and Performance Requirements (Annex I)

I. General Requirements

- Contains risk management requirement for each device covering the whole product life cycle (EN ISO 14971)

II. Requirements regarding performance, design and manufacturing , e.g.:

- Performance characteristics:
  - Analytical perf. char. (e.g. LoD, linearity, interference, cross-reactions)
  - Clinical perf. char. (e.g. Diagn. Sens./Spec. , PPV / NPV)
  - Requirements for self-testing or near-patient testing
- Chemical, physical and biological properties

……

III. Requirements regarding information supplied with the device

- Labelling
- IFU

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General Safety and Performance Requirements

Similar to current Essential Requirements as per Annex I IVDD, however more detailed now

Evidence for compliance with Annex I e.g. by means of:

- harmonised standards (Article 6)
- “Common specifications” (Article 7)

Device must represent the **“state of the art”** (to be indentified by the manufacturer, e.g. based on market information, literature, competitor products etc.)

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General Safety and Performance Requirements

GSPR#	Requirement	App.	Justification	Method	Standard	Evidence for compliance within the Technical Documentation
6.	The characteristics and performance of a device shall not be adversely affected to such a degree that the health or safety of the patient or the user and, where applicable, of other persons are compromised during the lifetime of the device, as indicated by the manufacturer, when the device is subjected to the stresses which can occur during normal conditions of use and has been properly maintained in accordance with the manufacturer's instructions.	Y	-	Stability studies (real-time, accelerated, in-use)	EN ISO 23640:2015 In vitro diagnostic medical devices - Evaluation of stability of in vitro diagnostic reagents CLSI EP25-A (2009) Evaluation of stability of in vitro diagnostic reagents	TD chapter 6 – Stability „stability_study_plan_product_XYZ_v02-00.pdf“ „stability_report_product_XYZ_v01-00.pdf“ …

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Technical Documentation

Requirements as per Annex II

1. Device Description and Specification, including variants and accessories

e.g. including:

- product or trade name and a general description
- UDI device identifier
- Intended use / Classification details
- Testing population / Target population (CDx only)
- Description of active incredients (e.g. antibodies, primers)
- Instrumentation / software involved

2. Information supplied by the manufacturer

e.g. including:

- labelling
- IFU

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Technical Documentation

Requirements as per Annex II

3. Design and Manufacturing Information

e.g. including:

- Information to support the understanding of design stages, such as:
  - Critical ingredients: antigens, AB, primers
  - Analytical technology, overview of entire system
  - In case of SW products: algorithm
  - For self-testing devices and POCT (point of care testing): specific design aspects making the device suitable

- Manufacturing information, such as:
  - Manufacturing processes
  - Manufacturing sites involved, including suppliers and sub-contractors

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Technical Documentation

Requirements as per Annex II

4. General Safety and Performance Requirements

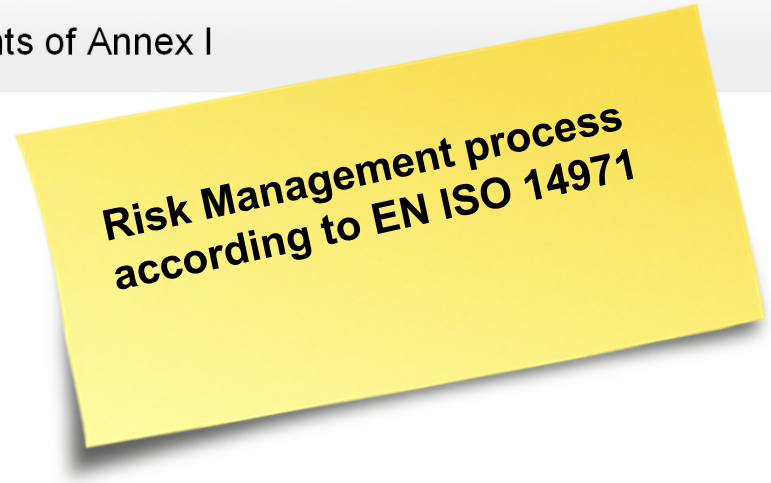
General demonstration of conformity with the general safety and performance:

Layout of applicable requirements / harmonized standards / CS

precise identity of the controlled documents offering evidence including cross-reference to the actual location within the TD

5. Risk / Benefit Analysis and Risk Management

Evidence for fulfillment of respective requirements of Annex I



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Technical Documentation

Requirements as per Annex II

6. Product Verification and Validation

Including:

- Information on analytical performance characteristics
- Information on clinical performance and clinical evidence
  - performance evaluation report, reports on the scientific validity, the analytic … performance
  - Documents shall be included and/or fully referenced

- Stability

- Software verification and validation

- Additional information in specific cases, e.g.:
  - Specific requirements for sterile devices (conditions for manufacturing, bioburden testing, pyrogen testing etc.
  - devices placed on the market with a measuring function (accuracy)

More detailed requirements for TDs defined now

More data and evidences to be maintained in the TD

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Precisely Right.

Technical Documentation

Requirements for economic operators

Article 10

(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 requirem
Regulation to be assessed. The technical documentation shall include the elemen d
III.

(7) Manufacturers shall keep the technical documentation, the EU decla
a copy of the relevant certificate, including any amendments and supple
Article 51, available for the competent authorities for a period of at least
by the EU declaration of conformity has been placed on the market. .

Business Impact, e.g. for PLMs ?

Need for Quality Agreements

Article 11:

(3b) Authorized representatives:

…keep available a copy of the technical documentation, the EU declaration of conformity and, if applicable, a copy of the relevant certificate, including any amendments and supplements…

Technical Documentation

„SSP“: Summary of safety and performance (Article 29)

Content:

- (a) the **identification of the device and the manufacturer**, **including the Basic UDI-DI** and, if already issued, the SRN;
- (b) the **intended purpose** of the device and any indications, contra-indications and target populations;
- (c) a **description of the device**, including a reference to previous generation(s) or variants ….
- (d) reference to **any harmonised standards and CS applied**;
- (e) the **summary of the performance evaluation** as referred to in Annex XIII, and relevant information on the PMPF;
- (f) the metrological **traceability of assigned values**;
- (g) suggested profile and training for users;
- (h) information on **any residual risks** and any undesirable effects, warnings and precautions.

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Precisely Right.

Technical Documentation

SSP Summary of safety and performance (Article 29)

- Summary report, separate to the TD
- Mandatory for **class C and D** products
- Shall be written in a way that is clear to the intended user and, if relevant, to the patient
- Shall be written in an official language of the country the product is sold
- Shall be made **available to the public via Eudamed** / after “verification” by the NB

To be updated continuously if necessary

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Precisely Right.

Technical Documentation

Sampling of TDs as per Annex VII, section 4.5.2 (Notified Body TD assessment)

As part of the QMS audit:

…draw up and keep up to date, for class B and class C devices, a sampling plan for the assessment of technical documentation as referred to in Annexes II and III covering the range of such devices covered by the manufacturer's application.

That plan **shall ensure that all devices** covered by the certificate are sampled over the period of validity of the certificate..

Article 48:

9. Manufacturers of **class B** devices….assessment of the technical documentation ….for at least one representative device **per category** of devices

7. Manufacturers of **class C** devices… assessment of the technical documentation.. of at least one representative device **per generic device group**

Clarification needed by the EC concerning “sampling” definition and basis for grouping

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Precisely Right.

Technical Documentation

NBOG Codes – NB Designation (+ TD sampling ?)

Multi-dimensional system:

I) Product Codes (8 main groups with various sub-codes)

II) Additional „Horizontal codes“

- „IVD specifics“: e.g. self-testing, near patient testing, CDx, SW
- Types of examination procedures: e.g. immunoassay, NAT/NGS,
- „Laboratory and clinical disciplines“: e.g. Virology, Histology, Clinical Chemistry
- Manufacturing technologies (audit): e.g. chemical processing, biotechnology, plastic processing

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Precisely Right.

Technical Documentation

NBOG Codes – NB Designation (+ TD sampling ?)

I) Product Codes (8 main groups with various sub-codes)

1. Blood grouping (e.g. ABO, Rhesus, Kell..)
2. Tissue typing (e.g. HLA)
3. markers of cancer and non-malignant tumours
4. Human genetic testing (e.g. congenital / inherited disorders , prognosis)
5. Infections / immune status
6. Physiological markers, non-infectious pathologies, disorders / impairments (e.g. congenital disorders, allergy, pregnancy and ovulation)
7. Controls without a quantitative or qualitative assigned value
8. Class A sterile

Technical Documentation

NBOG Codes –TD sampling – proposal TRLP

Product category / **Class B**

Generic device group / **Class C**

(5) Devices intended to be used to determine markers of infections / immune status

IVR CODE	**Devices intended to be used for the screening, confirmation, identification of infectious agents or determination of immune status**
IVR 0501	Devices intended to be used for pre-natal screening of women in order to determine their immune status towards transmissible agents
IVR 0502	Devices intended to be used to detect the presence of, or exposure to transmissible agents in blood, blood components, cells, tissues or organs, or in any of their derivatives, to assess their suitability for transfusion, transplantation or cell administration
IVR 0503	Devices intended to be used to detect the presence of, or exposure to an infectious agent including sexually transmitted agents
IVR 0504	Devices intended to be used to determine the infectious load, to determine infective disease status or immune status and devices used for infectious disease staging
IVR 0505	Devices intended to be used to grow / isolate / identify and handle infectious agents
IVR 0506	Other devices intended to be used to determine markers of infections / immune status

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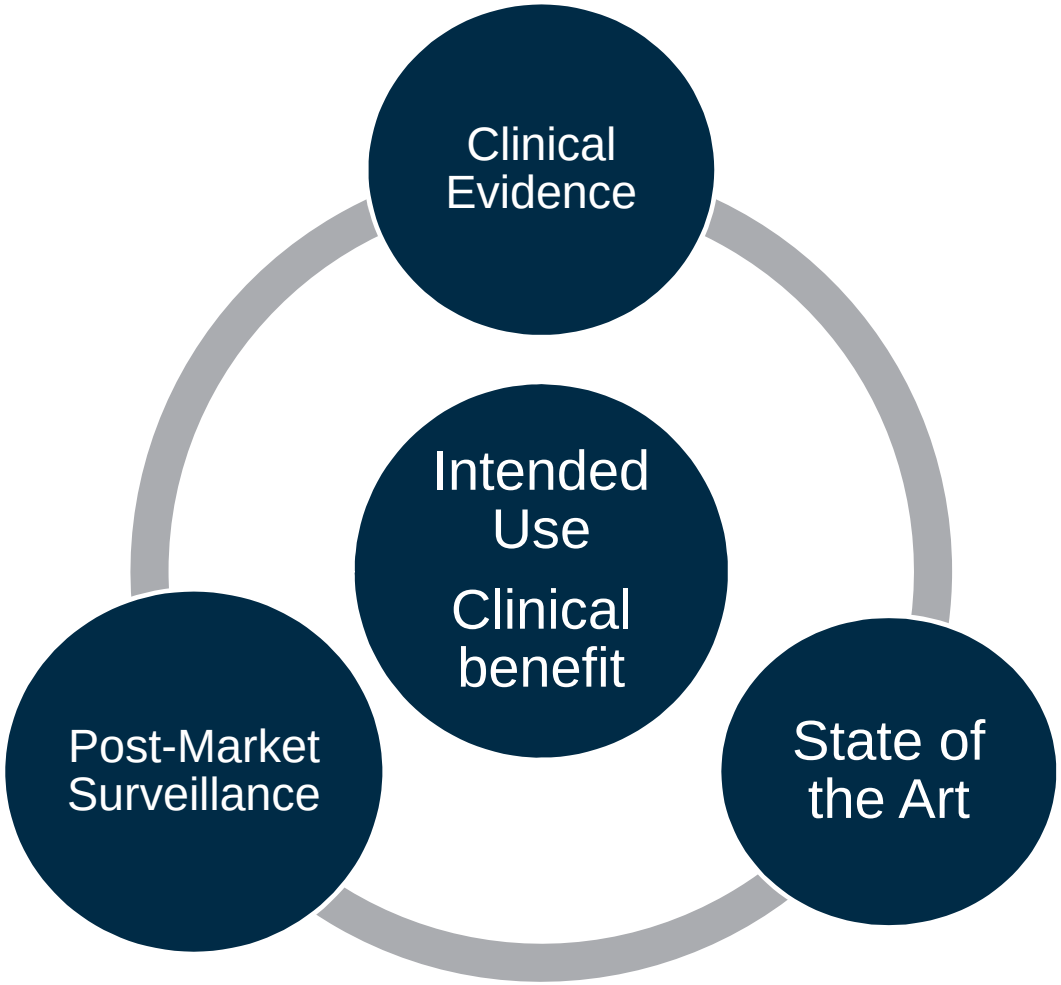
Precisely Right.

Clinical Evidence



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Precisely Right.

State of the Art

IVDD

Annex I+ IV

The solutions ….for the design and construction of the devices must

conform to safety principles, taking account of the generally acknowledged **state of the art**.

The manufacturer shall carry out the required controls and tests **according to the latest state of the art.**

IVDR

Article 56
Annex I
Annex XIII

The clinical evidence shall be such as to scientifically demonstrate, by reference to the **state of the art in medicine**, that the intended clinical benefit(s) will be achieved ….

In the case of clinical performance studies, the analytical performance has been demonstrated, taking into consideration **the state of the art.**

…. taking into account the generally acknowledged **state of the art.**

Risk control measures adopted by manufacturers for the design and manufacture of the devices shall conform to safety principles, taking account of the generally acknowledged **state of the art.**

…….

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Precisely Right.

State of the Art

IVDR

Annex XIII

Clinical performance study: its design type such as observational, interventional together with the objectives and hypotheses of the study, shall be according to the current state of the art in diagnosis and/or medicine

Performance evaluation plan shall include:

a description of the state of the art, including**:**

an identification of existing relevant standards, CS, Guidance, or best practices documents

--> According to current interpretation this includes also products of competitor (what was tested ? What was achieved)

To be reassessed continuously as part of the Post-Market Surveillance

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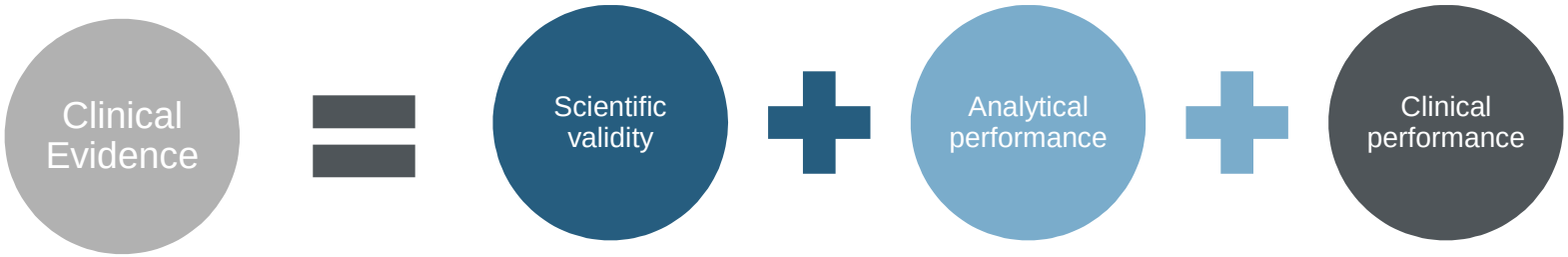
Precisely Right.

Clinical Evidence

Definition:
clinical data and performance evaluation results …. allow a qualified assessment of whether the device **is safe and achieves the intended clinical benefit(s)**, when used **as intended by the manufacturer**



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Precisely Right.

Clinical Evidence

Scientific validity

Definition:
'scientific validity of an analyte' means the association of an analyte with a clinical condition or a physiological state;

Analytical performance

Definition:
'performance of a device' means the ability of a device to achieve its intended purpose as claimed by the manufacturer.
'analytical performance' means the ability of a device to correctly detect or measure a particular analyte;

Clinical performance

Definition:
'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;

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Precisely Right.

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Precisely Right.

Performance Evaluation

Scientific Validity

Scientific validity

Sources:
IVDR – Annex XIII / 1.2.1
GHTF (now IMDRF) - SG5/N7:2012 Clinical evidence for IVD medical devices

- 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.

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Precisely Right.

Performance Evaluation

Scientific Validity

Scientific validity

Well established marker more likely through literature route (e.g. p24 antigen HIV, calcium)

For new (bio)markers scientific validity proven by means of the clinical study.

Legacy Products:
To be established !
Rephrasing of Intended Use necessary ?
Is the analyte/marker actually proven already ?

IVDD:
No similar requirement

TÜVRheinland®
Precisely Right.

Performance Evaluation

Analytical performance

Analytical performance

Characteristics to be established as per Annex I, section 9.1

- analytical sensitivity / limit of detection
- analytical specificity
  - handling and control of known relevant endogenous and exogenous interference
  - cross-reactions
- trueness (bias)
- precision (repeatability and reproducibility)
- accuracy (resulting from trueness and precision)
- limits of detection and quantitation
- measuring range
- Linearity
- cut-off
- including determination of appropriate criteria for specimen collection

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Precisely Right.

Performance Evaluation

Analytical Performance

Analytical performance

Examples of details required for Annex II Technical

Interferents and cross-reacting substances or agents, which vary greatly depending on the assay type and design, could derive from exogenous or endogenous sources such as:

- substances used for patient treatment such as medicinal products
- substances ingested by the patient such as alcohol, foods
- substances added during specimen preparation such as preservatives, stabilisers
- substances encountered in specific specimen types such as haemoglobin, lipids, bilirubin, proteins analytes of similar structure such as precursors, metabolites

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Precisely Right.

Performance Evaluation

Analytical Performance

Analytical performance

Examples of details required for Annex II Technical

Definition of assay cut-off

This Section shall provide a summary of analytical data with a description of the study design including methods for determining the assay cut-off, such as:

- the population(s) studied: demographics, selection, inclusion and exclusion criteria, number of individuals included
- method or mode of characterisation of specimens
- statistical methods such as Receiver O[illegible] (ROC) to generate results and if grey-zone/equivocal

IVDD:
Similar requirements, but not that detailed
Applied less strict
Not all characteristics stated in the IFU

Legacy Products:
Existing data can be used
…but is it sufficient ?

What is the current state of the art ?
Current standards and CS?
Data generated by competitor´s?
Current guidelines (e.g.CLSI) ?

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Precisely Right.

Performance Evaluation

Analytical Performance

Analytical performance

The manufacturer shall demonstrate the analytical performance of the device in relation to all the parameters ….. unless any omission can be justified as not applicable (e.g. linearity for qualitative assay).

As a general rule, the analytical performance shall always be demonstrated on the basis of analytical performance studies (in-house 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 …., 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.

Performance Evaluation

Clinical performance

Clinical performance

Characteristics to be established:

- diagnostic sensitivity
- diagnostic specificity
- positive predictive value
- negative predictive value
- likelihood ratio
- expected values in normal and affected populations

Performance Evaluation

Clinical performance

Clinical performance

Demonstration of the clinical performance of a device shall be bas
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**.

IVDD:
similar requirements but less detailed

Data to be generated in clinical environment or from literature

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Precisely Right.

Performance Evaluation

Clinical evidence – general comment

Clinical Evidence

The manufacturer shall specify and justify the level of the clinical evidence necessary to demonstrate conformity with the relevant general safety and performance requirements. That level of clinical evidence shall be appropriate in view of the characteristics of the device and its intended purpose.

→ risk based approach

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Precisely Right.

Performance Evaluation

Performance evaluation of a device is a continuous process by which data are assessed and analysed to demonstrate the scientific validity, analytical performance and clinical performance of that device for its intended purpose as stated by the manufacturer.

Deliverables defined in Annex XIII, Part A:

Performance Evaluation Plan, which shall include e.g.:

- a specification of the characteristics of the device as described in Annex I
- a specification of the analyte or marker to be determined by the device
- a specification of the intended use of the device
- identification of certified reference materials or reference measurement proc
  traceability
- a clear identification of specified target patient groups with clear indications, limitations and contra- indications
- an identification of the general safety and performance requirements (incl. analytical / clinical performance) as laid down in Annex I

Inputs:
State of the art ?
Current standards and CS?
Data generated by competitor´s?
Current guidelines (e.g.CLSI) ?

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Precisely Right.

Performance Evaluation

Deliverables defined in Annex XIII, Part A:

Performance Evaluation Plan, continued.:

- a specification of methods, including the appropriate statistical tools, used for the examina
- a description of the state of the art
- an indication and specification of parameters to be used to determine the acceptability of the benefit-risk ratio for the intended purpose
- for software qualified as a device, an identification and specification of reference databases and other sources of data used as the basis for its decision making
- an outline of the different development phases …..including an indication of milestones and a description of potential acceptance criteria
- the **Post-Market Performance Follow up (PMPF)** planning as referred to in Part B of this Annex.

- Where any of the above mentioned elements are **not** deemed appropriate in the Performance Evaluation Plan due to the specific device characteristics a justification shall be provided in the plan.

IVDD:
no specific planning requirements
EN 13612

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Precisely Right.

Performance Evaluation

Deliverables defined in Annex XIII, Part A:

Performance Evaluation Report, which 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

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Precisely Right.

Performance Evaluation

Clinical performance study

Clinical performance study plan (CPSP) :

It shall contain e.g.:

- information on the investigator or investigators, namely principal, coordinating or other investigator; qualifications; contact details, and investigation site or sites, such as number, qualification, contact details and, in the case of devices for self-testing, the location and number of lay persons involved

- information about the type of specimens under investigation

- overall synopsis (overview) of the clinical performance study, its design type, such as observational, interventional, together with the objectives and hypotheses of the study, reference to the current state of the art in diagnosis and/or medicine

- a description of the expected **risks and (clinical) benefits** of the device and of the clinical performance study in the context of the state of the art in clinical practice, and with the exception of studies using left-over samples, the medical procedures involved and patient management

Performance Evaluation

Clinical performance study

Clinical performance study plan (CPSP), continued **:**

- description of and justification for the design of the clinical performance study, its scientific robustness and validity, including the statistical design, and details of measures to be taken to minimise bias, such as randomisation, and management of potential confounding factors

- the **analytical performance** in accordance with point (a) of Section 9.1 of Chapter I of Annex I with justification for any omission

- parameters of clinical performance in accordance with point (b) of Section 9.1 of Annex I to be determined, with justification for any omission; and with the exception of studies using left-over samples the specified clinical outcomes/endpoints (primary/secondary) used with a justification and the potential implications for individual health and/or public health management decisions;

- information on the performance study population: specifications of the subjects, selection criteria, size of performance study population, representativity of target population and, if applicable, information on vulnerable subjects involved, such as children, pregnant women, immuno-compromised or elderly subjects

Performance Evaluation

Clinical performance study

Clinical performance study plan (CPSP), continued **:**

- criteria and procedures for suspension or early termination of the clinical performance study
- bibliography

IVDD:
Only few requirements for clinical studies
EN 13612

Legacy Products:
Existing data can be used
…but is it sufficient ?

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Precisely Right.

Performance Evaluation

Clinical performance study

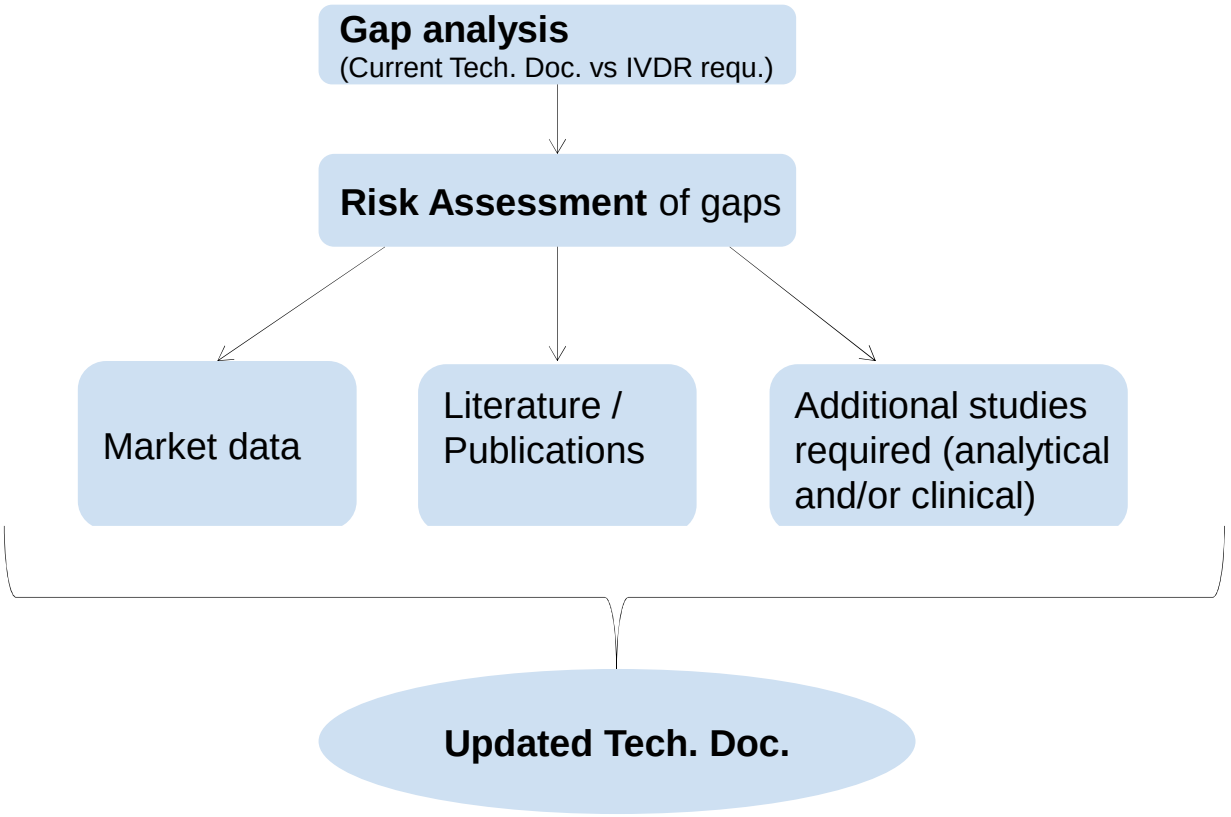
Clinical performance study report:

A clinical performance study report, signed by a medical practitioner or any other authorised person responsible, shall contain:

- documented information on the clinical performance study protocol plan
- results and conclusions of the clinical performance study, including negative findings
  The results and conclusions shall be transparent, free of bias and clinically relevant.
- 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.

Performance Evaluation

Legacy Products - Proposal



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Precisely Right.

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Precisely Right.

Post-Market Surveillance

Requirements as per Article 78, 79 / Annex III (Technical Documentation)

Post-market system to be established proportionate to the product risk / continuous process

PMS plan
shall address the collection and utilisation of available information:

- information concerning **serious incidents, non-serious incidents** and data on any undesirable side-effects
- relevant specialist **or technical literature, databases** and/or registers
- information, **including feedbacks and complaints**, provided by users, distributors and importers
- publicly-available information about **similar medical devices**.
- **Includes PMPF plan**

Post-Market Surveillance Report („PMSR“):

- To be prepared for **class A and class B** devices
- Summarizing the results of the PMS
- to be updated when necessary
- to be provided to the Notified Body **upon request**

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Precisely Right.

Post-Market Surveillance

Periodic Safety Update Report („PSUR“)

Periodic Safety Update Report („PSUR“):
shall contain:

- the results and conclusions of the analyses of the **post-market surveillance data (PMS)**
- the conclusions of the **benefit-risk determination**
- the main findings of the **Post-Market Performance Follow up (“PMPF”)**
- Volume of sales and other characteristics of the populations using the device

Periodic Safety Update Report („PSUR“):

- To be prepared for **class C and class D** devices
- to be **prepared / updated annually**
- to be provided to the Notified Body
- for **class D devices** the NB has to evaluate the PSUR

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Precisely Right.

Post-Market Surveillance

Post-Market Performance Follow Up (PMPF)

Article 56

The performance evaluation and its documentation shall be updated throughout the life cycle

Post-Market Performance Follow Up (PMPF) Plan has the aim of e.g.:

- confirming the safety and performance of the device throughout its expected lifetime
- identifying previously unknown risks or limits to performance and contra-indications
- ensuring the continued acceptability of the clinical evidence and of the benefit-risk ratio

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Precisely Right.

Post-Market Surveillance

Post-Market Performance Follow Up (PMPF)

PMPF plan shall include e.g.:

- the general methods and procedures of the PMPF to be applied such as:
  - gathering of clinical experience gained, feedback from users, screening of scientific literature and of other sources of performance or scientific data
  - ring trials and other quality assurance activities, epidemiological studies, evaluation of suitable patient or disease registers, genetic databanks or post-market clinical performance studies;
- a reference to the relevant parts of the performance evaluation report

PMPF evaluation report to be created that shall update the performance evaluation report and be part of the technical documentation.

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Precisely Right.

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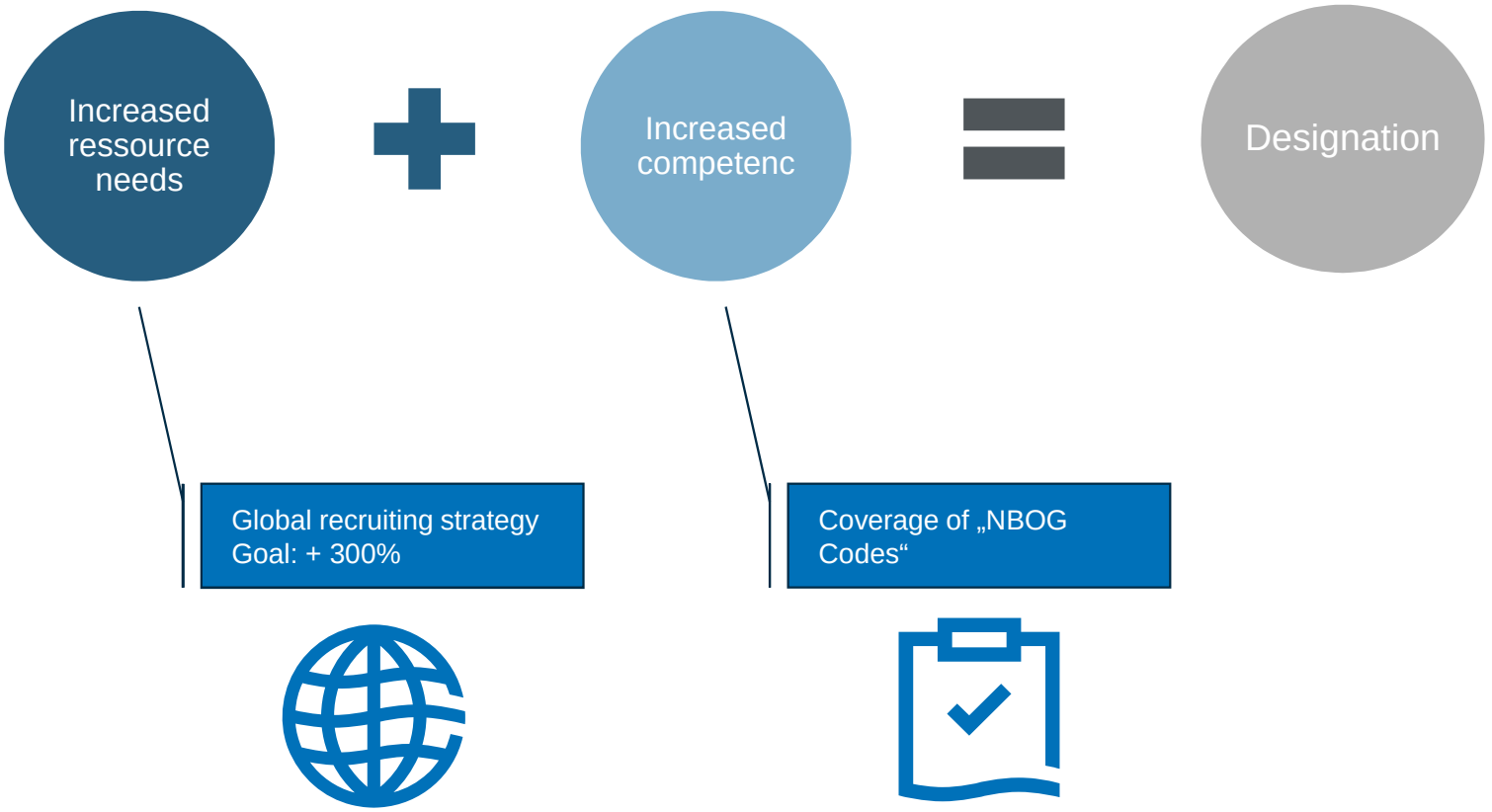
Precisely Right.

Impact on NBs



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Precisely Right.

Impact on NBs - Designation

NBOG Codes – IVDD

Product groups:
7 groups for List A products , e.g.:
- IVD 0101 ABO system
- IVD 0201 HIV infection

9 groups for list B products , e.g.:
- IVD 0305 Human infections: CMV+Chlamydia
- IVD 0306 HLA tissue groups: DR, A, B

6 groups for self testing devices , e.g.:
- IVD 0405 Pregnancy and ovulation

"Horizontal codes":
6 codes "IVD specifics" , e.g. :
- MDS 7208 IVDs utilising nanomaterials
- MDS 7206 IVDs in sterile condition

NBOG Codes – IVDR

Product groups:
33 groups (divided into 8 p
- IVR 0101 Devic … determine markers of the ABO system
- IVR 0502 Devices intended to be used to detect the presence of … transmissible agents in blood…to assess their suitability for transfusion…

"Horizontal codes":
- 10 codes "Specific chara… CDx)
- 11 codes "Specific techn… manufacturing (e.g. biote… processing)
- 14 codes "Examination procedures" (e.g. immuno-assays, molecular biological testing, flow cytometry)
- 12 codes "Laboratory and clinical disciplines" (e.g. bacteriology, clinical chemistry, genetics)

In practice the product range increased by far more then 100 % as product groups are „wider" now

Very significant increase of number of horizontal codes (6 vs. 47)

Partially the meaning and related competence requirement is still unclear (e.g. clinical expertise)

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Precisely Right.

Impact on NBs - Designation

NBOG Codes – NB Designation + TD sampling

Multi-dimensional system:

I) Product Codes (8 main groups with various sub-codes)

II) Additional „Horizontal codes“

- „IVD specifics“: e.g. self-testing, near patient testing, CDx, SW
- Types of examination procedures: e.g. immunoassay, NAT/NGS,
- „Laboratory and clinical disciplines“: e.g. Virology, Histology, Clinical Chemistry
- Manufacturing technologies (audit): e.g. chemical processing, biotechnology, plastic processing

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Precisely Right.

Impact on NBs - Designation

NBOG Codes – „IVD specifics“

Additional competence requirements for NB

to be assigned for each TD assessment if applicable

(1) Specifics of in vitro diagnostic medical devices

CODE	IVDR specifics
001	Devices intended to be used for near-patient testing
02	Devices intended to be used for self-testing
3	Devices intended to be used as companion diagnostics
	Devices utilizing material of human origin
IVS 1005	Devices in sterile condition
IVS 1006	Calibrators (Annex VIII 1.5)
IVS 1007	Control materials with quantitative or qualitative assigned values intended for one specific analyte or multiple analytes (Annex VIII 1.6)
IVS 1008	Instruments, equipment, systems or apparatus
IVS 1009	Software independent of any other device including software apps, software for data analysis, and for defining or monitoring therapeutic measures
IVS 1010	Devices incorporating software / utilising software / controlled by software

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Precisely Right.

Impact on NBs - Designation

NBOG Codes – Types of examination procedures

Additional competence requirements for NB

to be assigned for each TD assessment if applicable

(3) Types of examination procedures – product verification

IVDP CODE	IVDR types of examination procedures
IVP 3001	Agglutination tests
IVP 3002	Biochemistry
IVP 3003	Chromatography
IVP 3004	Chromosomal analysis
IVP 3005	Coagulometry
IVP 3006	Flow cytometry
IVP 3007	Immunoassays
IVP 3008	Lysis based testing
IVP 3009	Measurement of radioactivity
IVP 3010	Microscopy
IVP 3011	Molecular biological testing including nucleic acid assays and next generation sequencing (NGS)
IVP 3012	Physical chemistry including electrochemistry
IVP 3013	Spectroscopy
IVP 3014	Tests of cell function

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Precisely Right.

Impact on NBs - Designation

NBOG Codes – „Laboratory and clinical disciplines“

Clinical expertise of NBs explicitely required

to be assigned for each TD assessment if applicable

IVP CODE	In vitro diagnostic devices which require specific knowledge in laboratory and clinical disciplines for the purpose of product verification
IVD 4001	In vitro diagnostic devices which require knowledge regarding bacteriology
IVD 4002	In vitro diagnostic devices which require knowledge regarding clinical chemistry / biochemistry
IVD 4003	In vitro diagnostic devices which require knowledge regarding detection of transmissible agents (without organisms or viruses)
IVD 4004	In vitro diagnostic devices which require knowledge regarding genetics
IVD 4005	In vitro diagnostic devices which require knowledge regarding haematology / haemostasis, including coagulation disorders
IVD 4006	In vitro diagnostic devices which require knowledge regarding histocompatibility and immunogenetics
IVD 4007	In vitro diagnostic devices which require knowledge regarding immunohistochemistry / histology
IVD 4008	In vitro diagnostic devices which require knowledge regarding immunology
IVD 4009	In vitro diagnostic devices which require knowledge regarding molecular biology / diagnostics
IVD 4010	In vitro diagnostic devices which require knowledge regarding mycology
IVD 4011	In vitro diagnostic devices which require knowledge regarding parasitology
IVD 4012	In vitro diagnostic devices which require knowledge regarding virology

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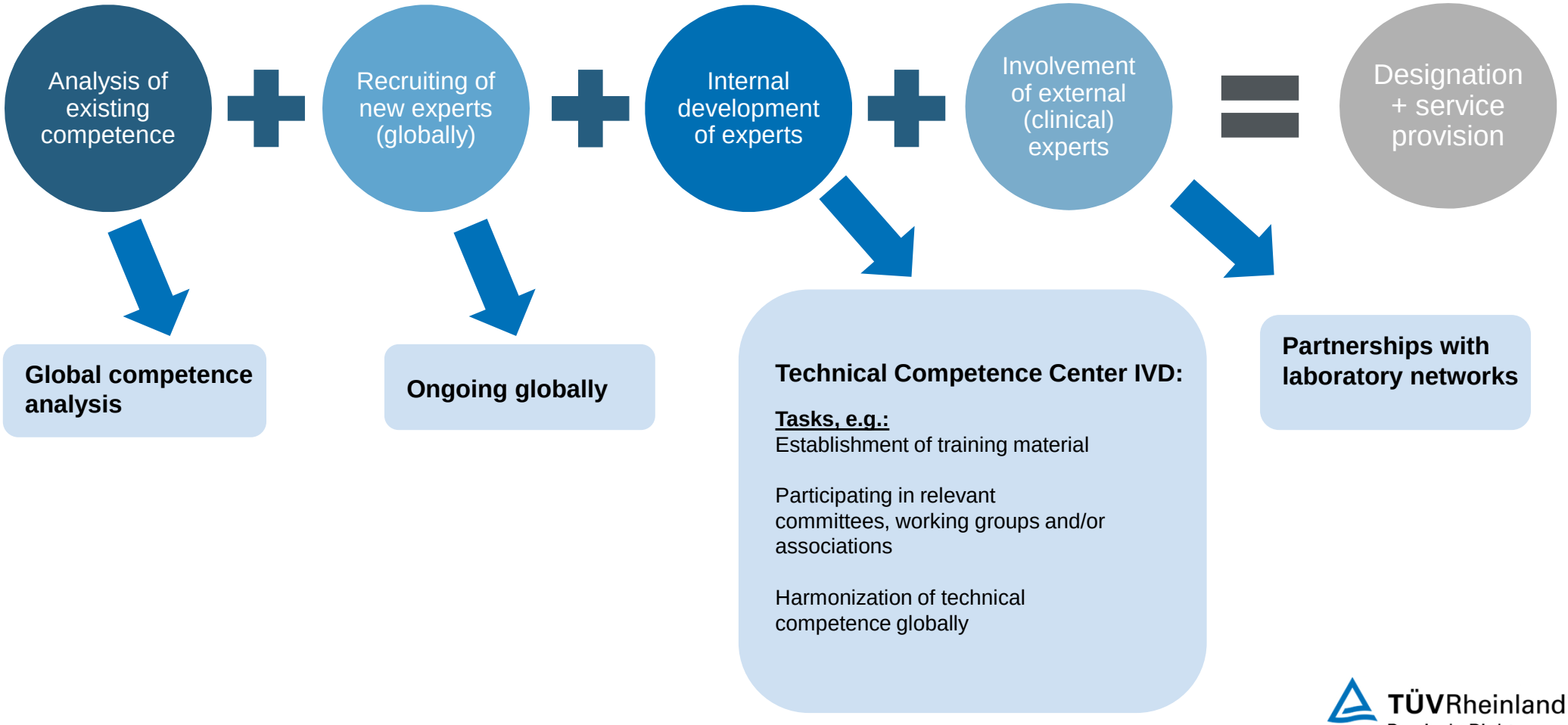
Precisely Right.

Impact on NBs - Strategy



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Precisely Right.

Impact on NBs - Designation – Strategy

Close colaboration with all stakeholders

Notified Body working groups („IVD Working Group“ / „Team NB“ / „IG NB“)

Manufacturer associations (VDGH / MedTech Europe)

Close contact to (designating) authorities through EK-MED, NB-MED, NAKI (TRLP will be the representative for the German NB)

Global project team established to implement IVDR requirements and to prepare a reliable application for designation

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Precisely Right.

Recommendations

- Familiarize yourself with the IVDR
- See how your business model (PLM) and product portfolio is affected by the IVDR

- Carry out a gap analysis for your products (Clinical Evidence / Technical Documentation)
- Update your quality management system processes (e.g. PMS, Vigilance, Risk Management)
- Establish a transition plan

- Carefully select your Notified Body (Scope ? Resources ?)
- Get in touch with your Notified Body already to discuss transition scenarios (e.g. legacy products) and timelines
- Start with a certification according to EN ISO 13485

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Precisely Right.

Thank you very much for your attention!

Any further questions ?

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