IVDR Workshop
LISAvienna Business Treff,
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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)

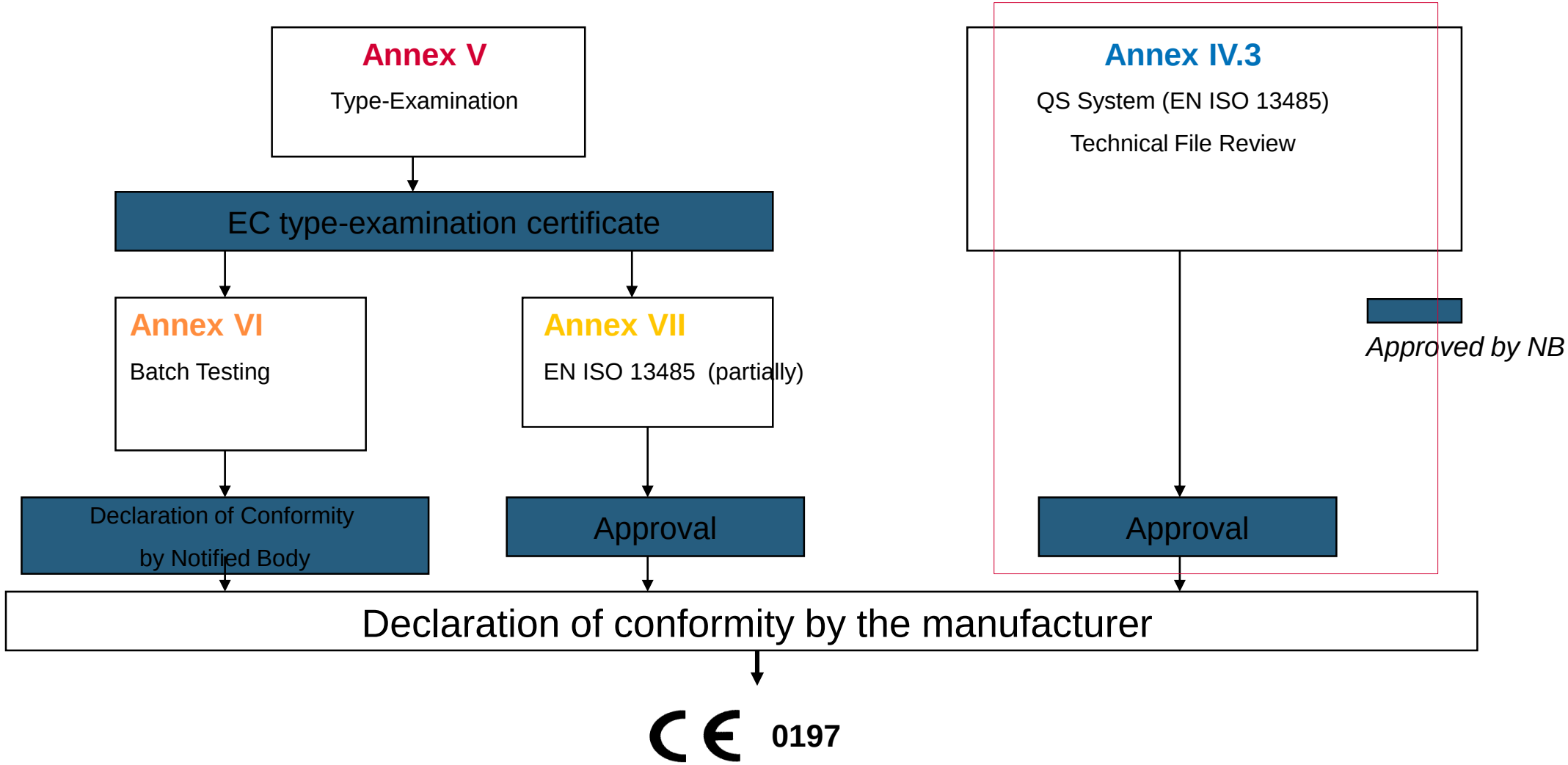
- *Blood Groups*
- AB0 system
- rhesus (C,c ,D ,E ,e)
- anti-Kell

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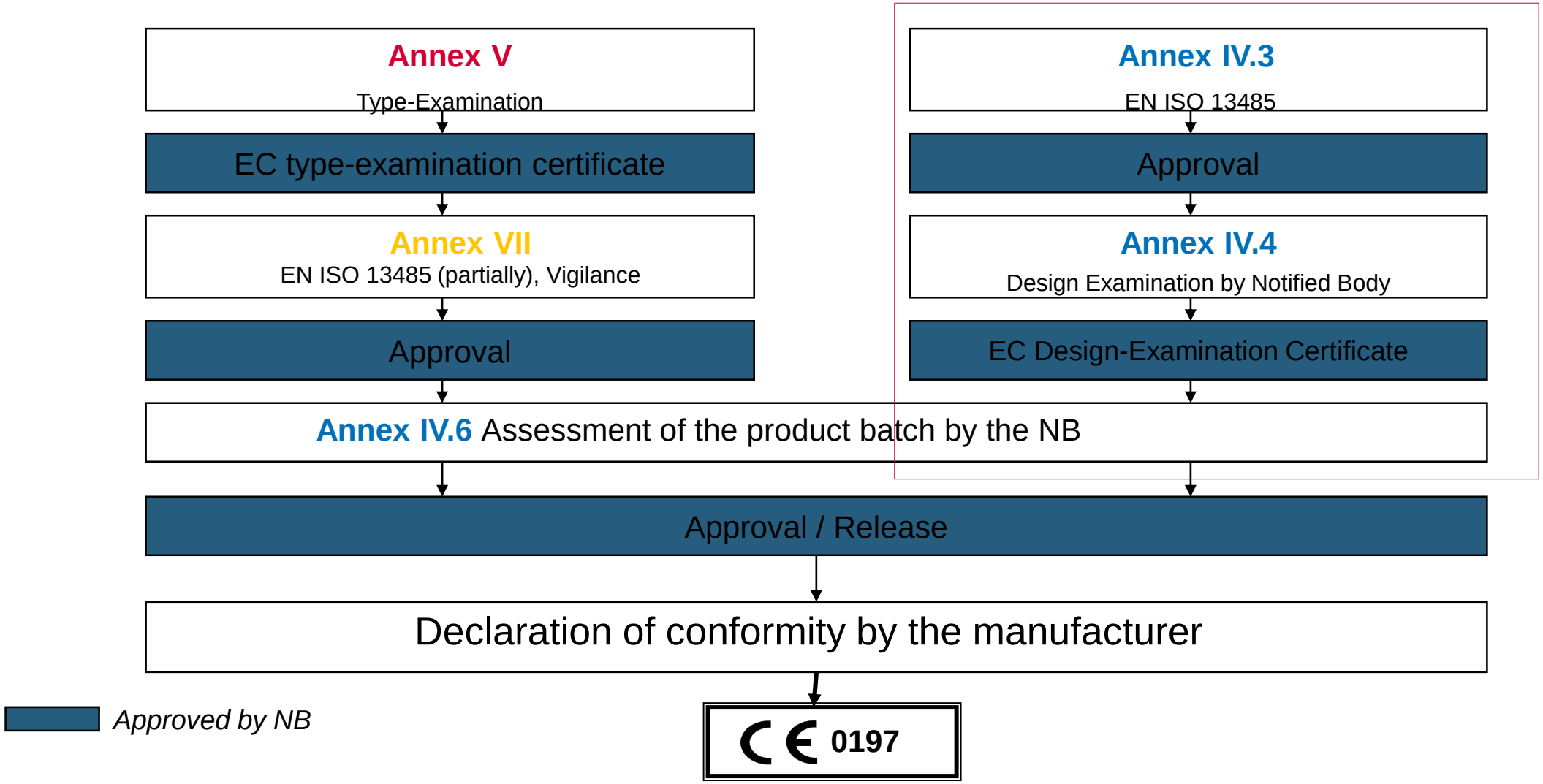
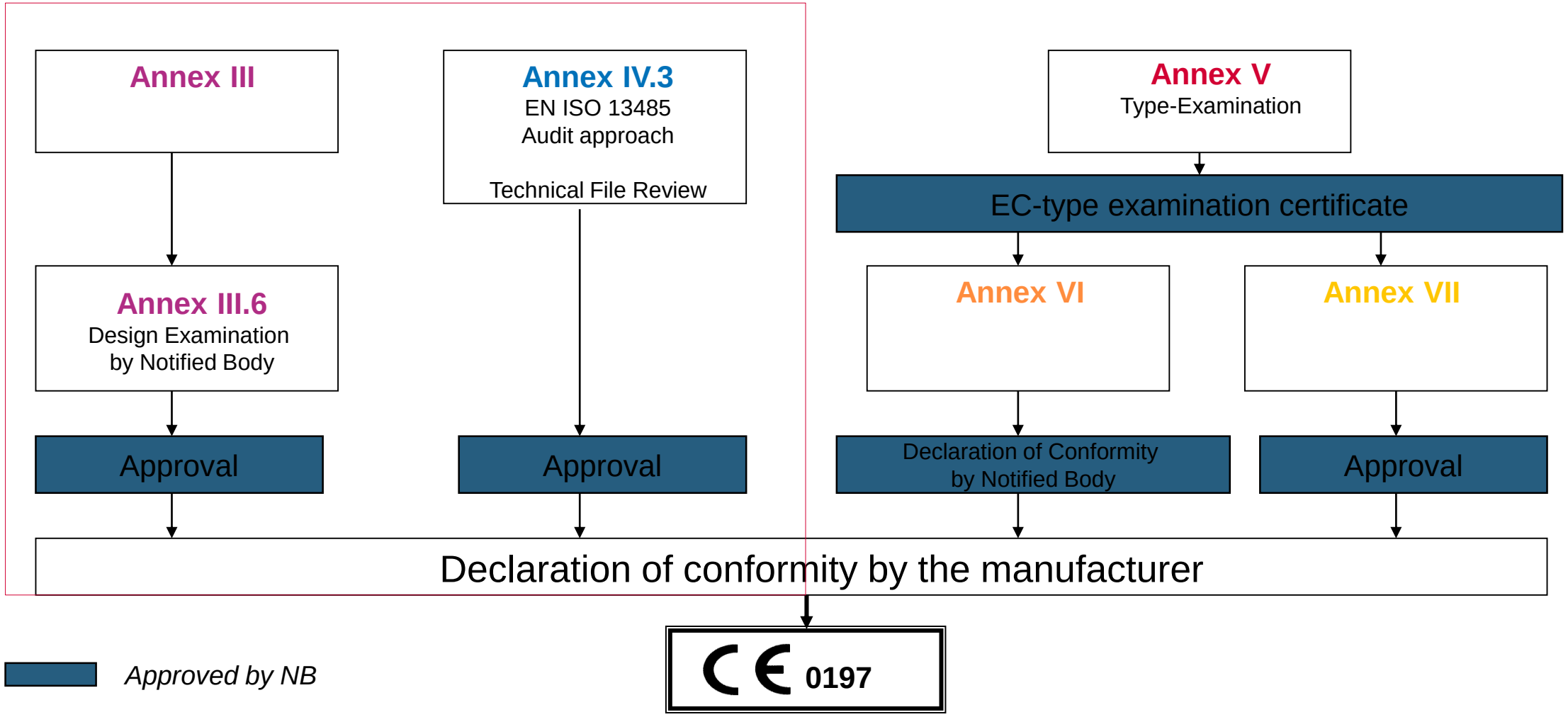
IVD Directive 98/79/EC - Conformity Assessment – Annex II List A



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



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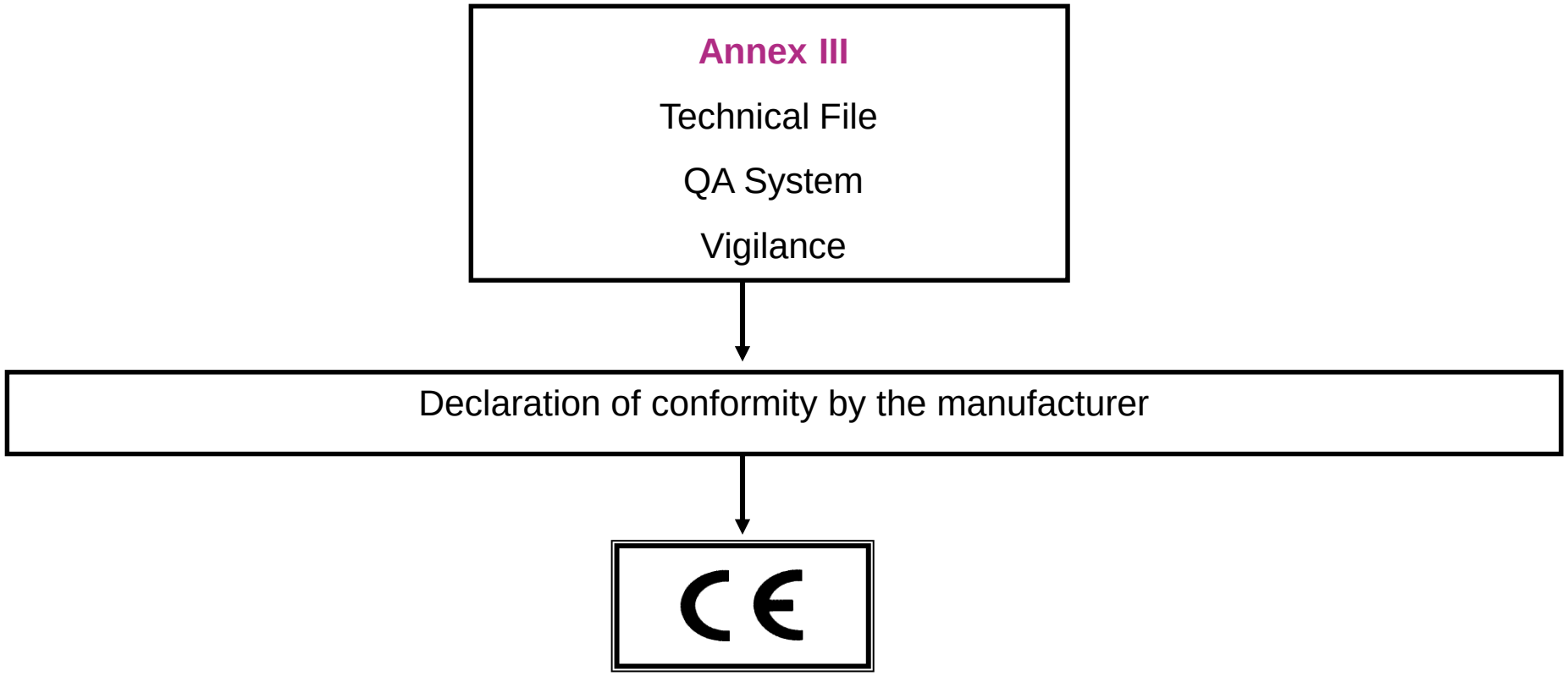
IVD Directive 98/79/EC - Conformity Assessment – “other IVDs”



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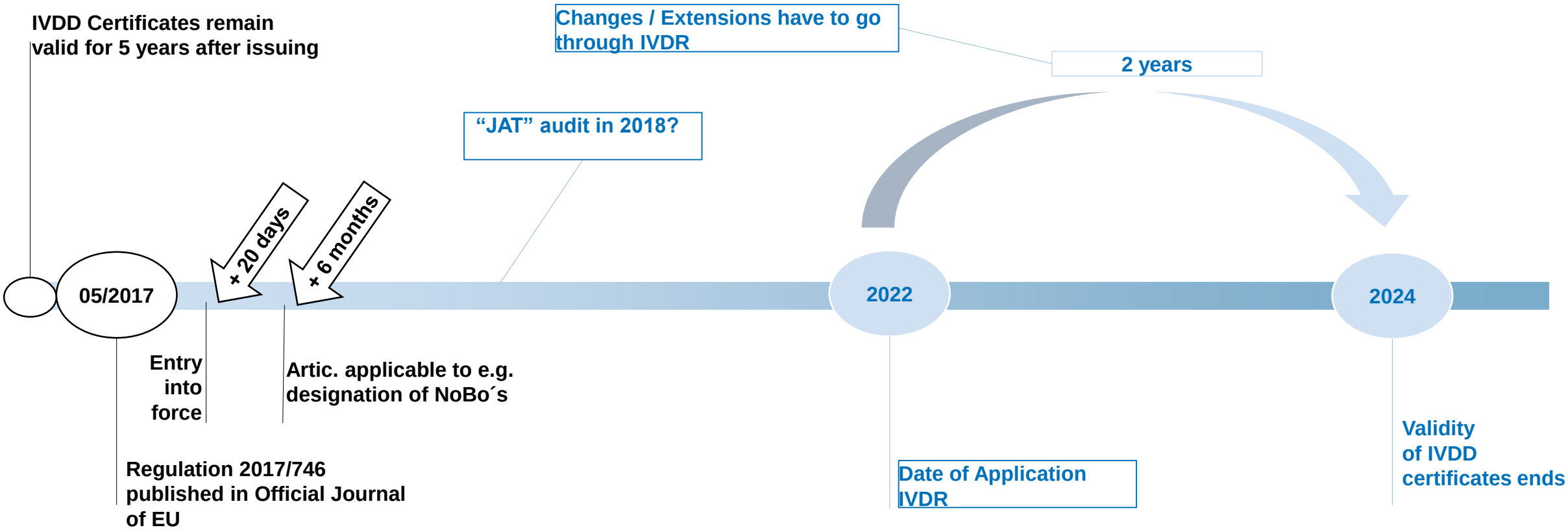
Overview - Transition Period

Transition Times



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Overview

Designation Process

- **Product scopes („NBOG codes“)** NoBo can apply for to become designated, are drafted
- will be defined by means of an implementing act **within 6 month** after IVDR entered into force
- as per the EU Commision the entire designation process may take **up to 18 to 24 month**

→ First conformity assessments under the IVDR possible **after 06/2019 presumably ?**

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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

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**.

Overview

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 database 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, Expert Laboratories, Expert Panels and Device Registers**
- Chapter IX Confidentiality, data protection, funding, penalties
- Chapter X Final provisions

Overview

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 Rules**
- **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, performance Studies and Post-Market Performance follow-up**
- **Annex XIV Clinical Performance studies and certain other performance studies**
- Annex XV Correlation Table

Overview

Economic operators

Manufacturer

means the 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 his name or trademark;

Importer

means any natural or legal person established within the Union who places a device from a third country on the Union market

Distributor

means any natural or legal person in the supply chain, other than the manufacturer or the importer, who makes a device available on the market

Economic operators

means the manufacturer, the authorised representative, the importer and the distributor

Overview

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

- Full traceability in both directions (Art. 25)
- Obligation to cooperate in case of enquiries by Competent Authorities or requests for corrective actions and 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!)

Overview

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

- Conformity of the imported product (Duty to verify CE mark, correct labelling (UDI) and existance of IFU)
- Obligation to record complaints, non-conforming products and recalls and to inform the legal manufacturer / authorized rep.
- **Importer to be indicated on the device or packaging or accompanying document**
- Verification of registration in EUDAMED

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

- Duty to verify CE mark, correct labelling (UDI) and existance of IFU (indication of importer) --> **sampling approach acceptable**
- Obligation to record complaints, non-conforming products and recalls and to inform the legal manufacturer / authorized rep. / importer
- Provision of free-of-charge product samples to CA

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
- ……, the authorised representative shall be **legally liable** for defective devices on the same basis as, jointly and severally, with the manufacturer.

Overview

Article 15 - Person responsible for regulatory compliance

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

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

Responsibilities:

- 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…
- post-market surveillance obligations fulfilled
- reporting obligations as part of the vigilance system
- The person…. shall suffer no disadvantage within the manufacturer's organisation.

Exemption for small companies

Hopefully !!

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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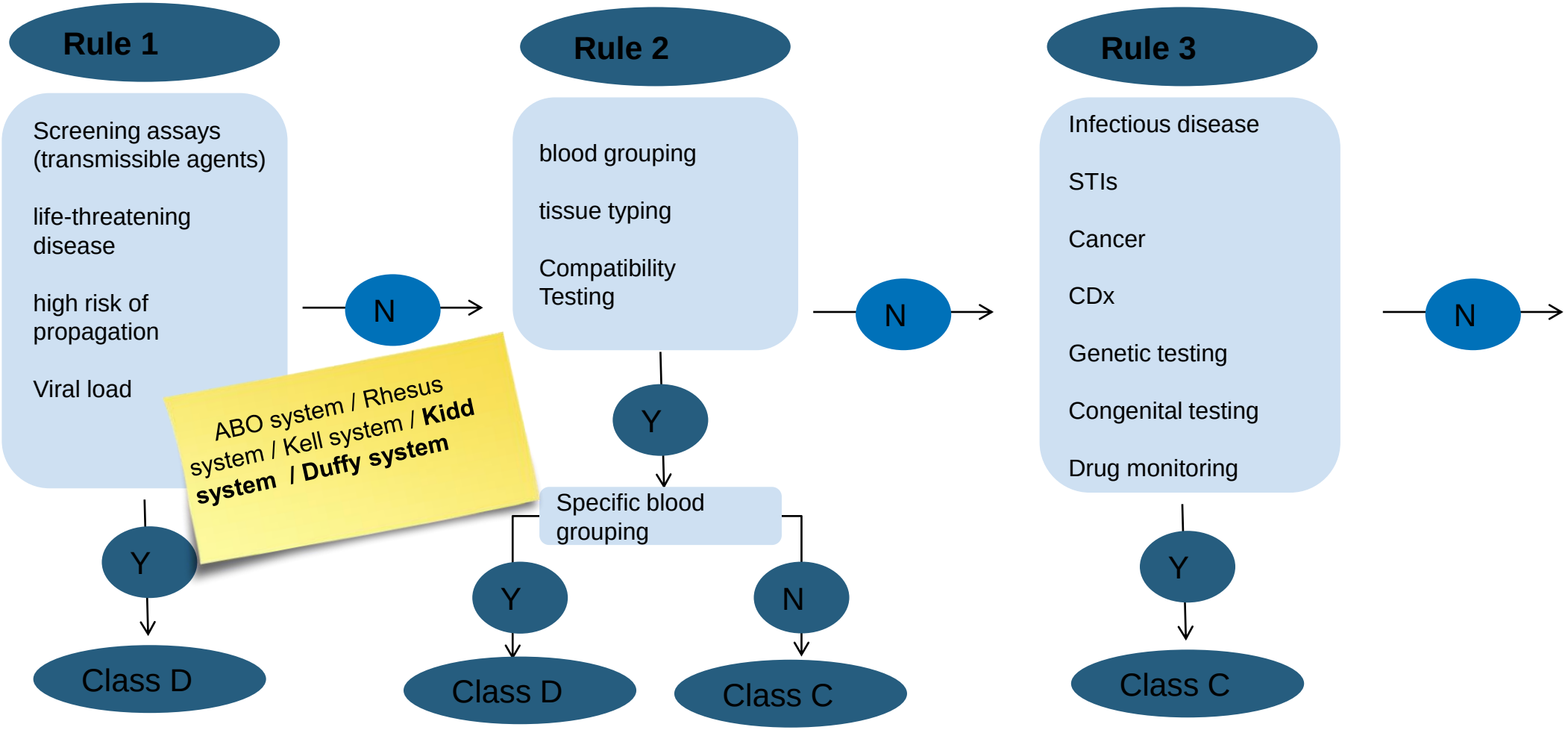
Classification

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**

Classification



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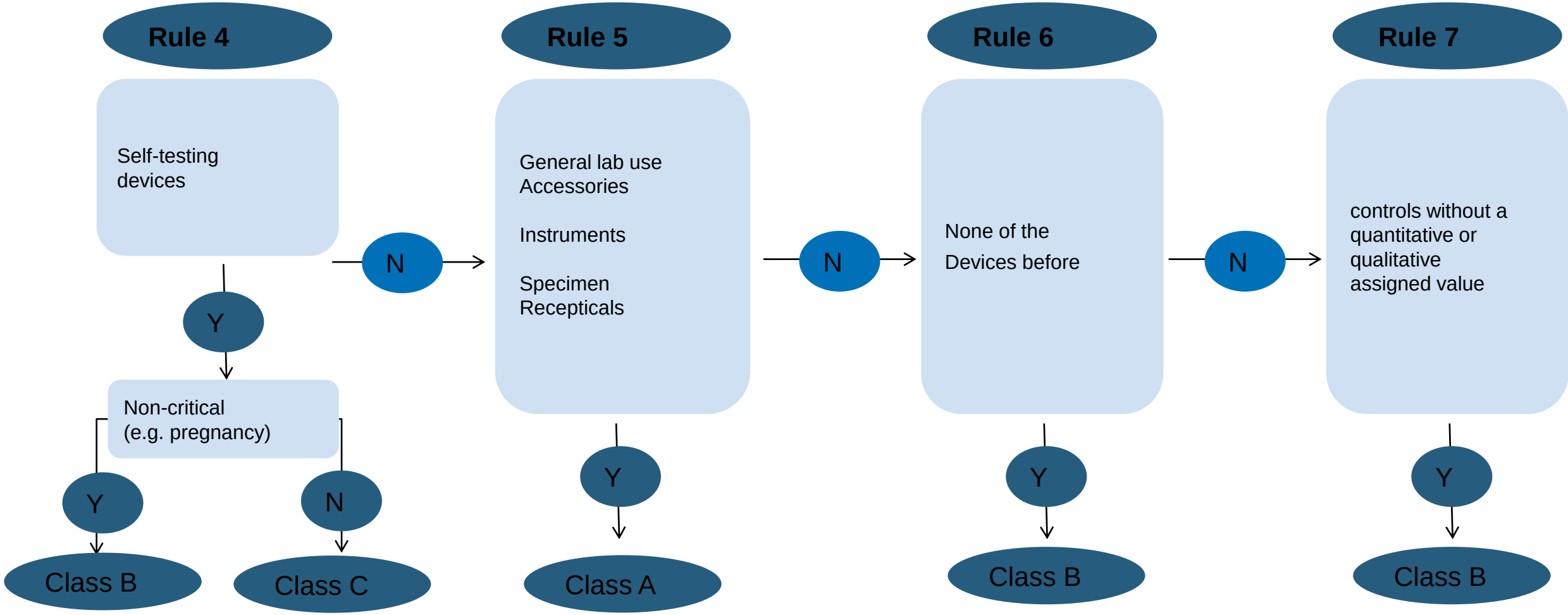
Classification



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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)

Classification

Impact of new classification

2017

IVD products
NoBo non-obligatory

IVD products
NoBo obligatory

2022

IVD products
NoBo non-obligatory

IVD products
NoBo obligatory

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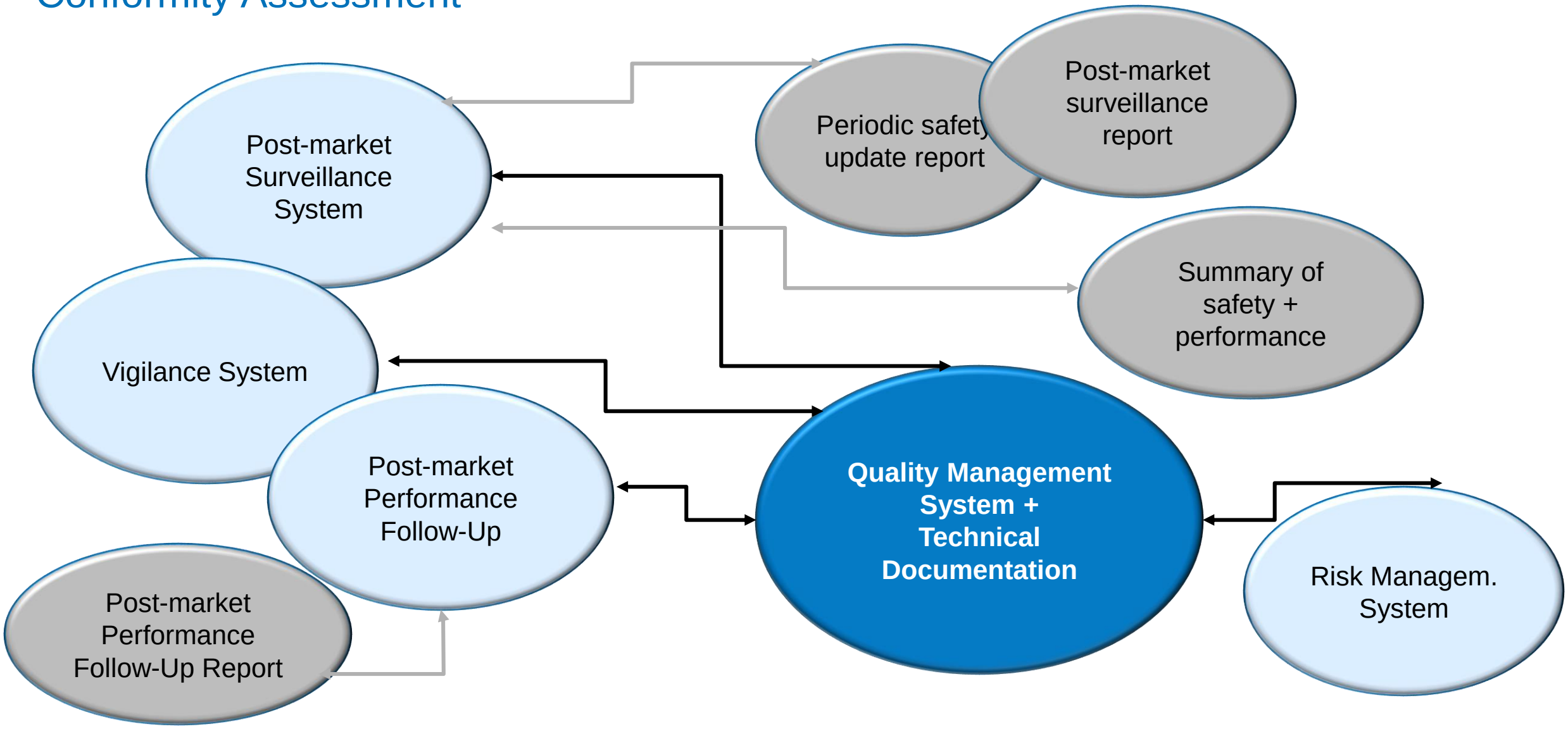
Conformity Assessment



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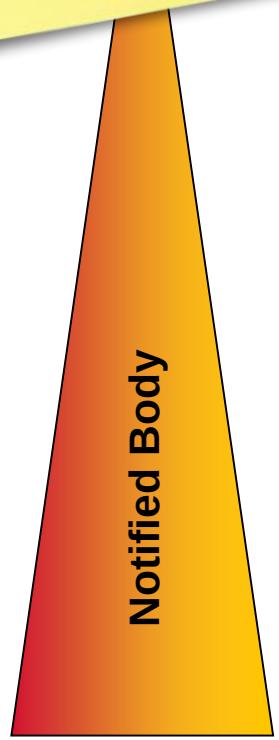
Conformity Assessment procedures

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***

- No conformity assessment any longer equivalent to:
- Annex VI IVDD
- Annex III.6 IVDD



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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

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)

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 allowed?

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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 unclear

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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Conformity Assessment - Companion diagnostics (CDx)

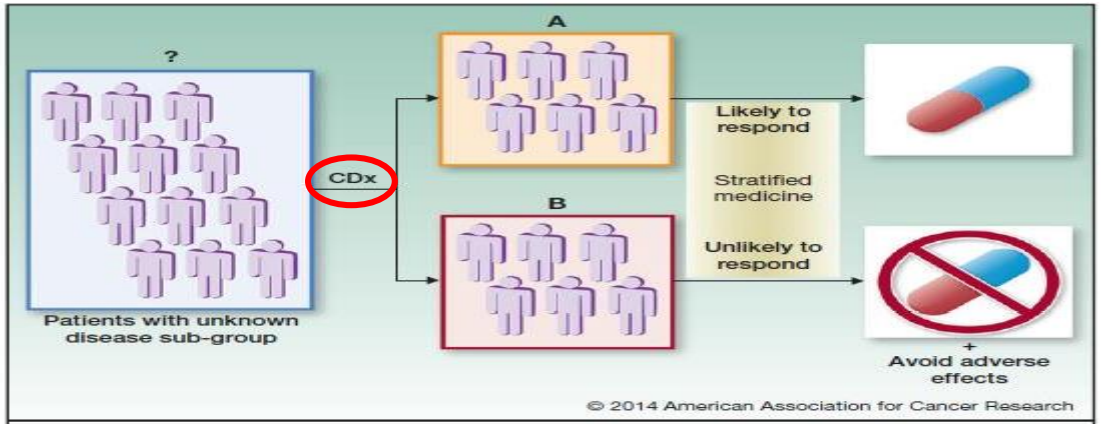
Definition CDx (IVDR)

A device which is **essential for the safe and effective use of a corresponding medicinal product** to:

(a) identify, before and/or during treatment, patients who are most likely to benefit from the corresponding medicinal product; or

(b) identify, before and/or during treatment, patients likely to be at increased risk of serious adverse reactions as a result of treatment with the corresponding medicinal product

Companion diagnostics (CDx)



Use of a companion diagnostic (CDx) to identify the patient subgroup suitable for treatment with the corresponding pharmaceutical. Moreover, CDx-guided stratification avoids adverse effects from the treatment in those who are unlikely to benefit.

TÜV Rheinland Business Plan – Strategy 2020

FDA definition CDx:
An IVD companion diagnostic device is an in vitro diagnostic device **that provides information** that is essential for the safe and effective use of a corresponding therapeutic

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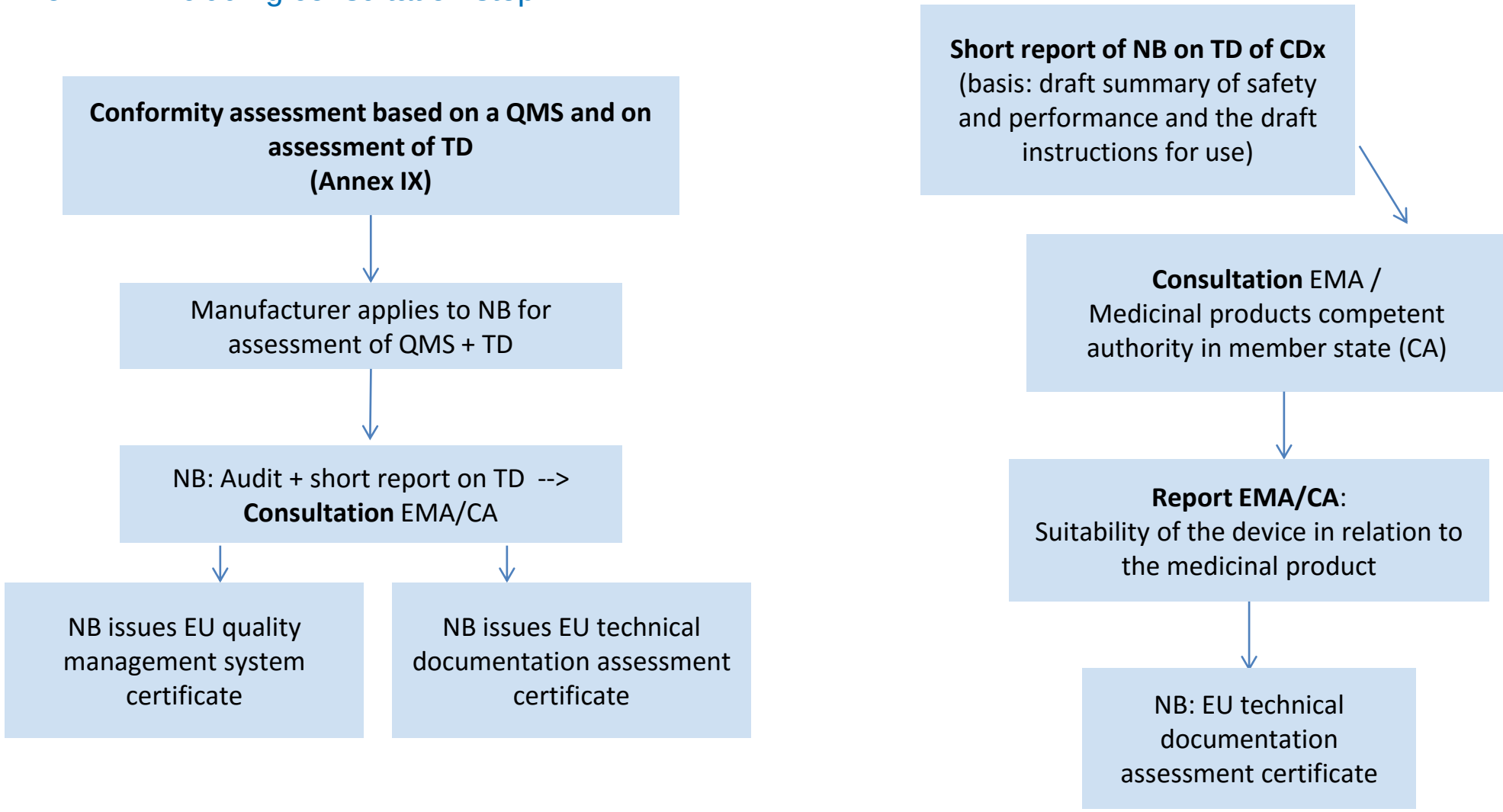
Conformity Assessment - Companion diagnostics (CDx)

Annex IX – including consultation step



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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)
  - Traceability
  - Requirements for self-testing or near-patient testing
- Chemical, physical and biological properties
- Infection and microbial contamination (risk of infection for the user)

III. Requirements regarding information supplied with the device

- Labelling
- IFU

General Safety and Performance Requirements

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

To comply with Annex I application and fulfillment of:

- harmonised standards (Article 6)
- “Common specifications” (Article 7)
- Device must represent the “state of the art”

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 purpose / 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

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

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

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… …linical 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

Full TD to be maintained by the legal manufacturer (includes PLMs)

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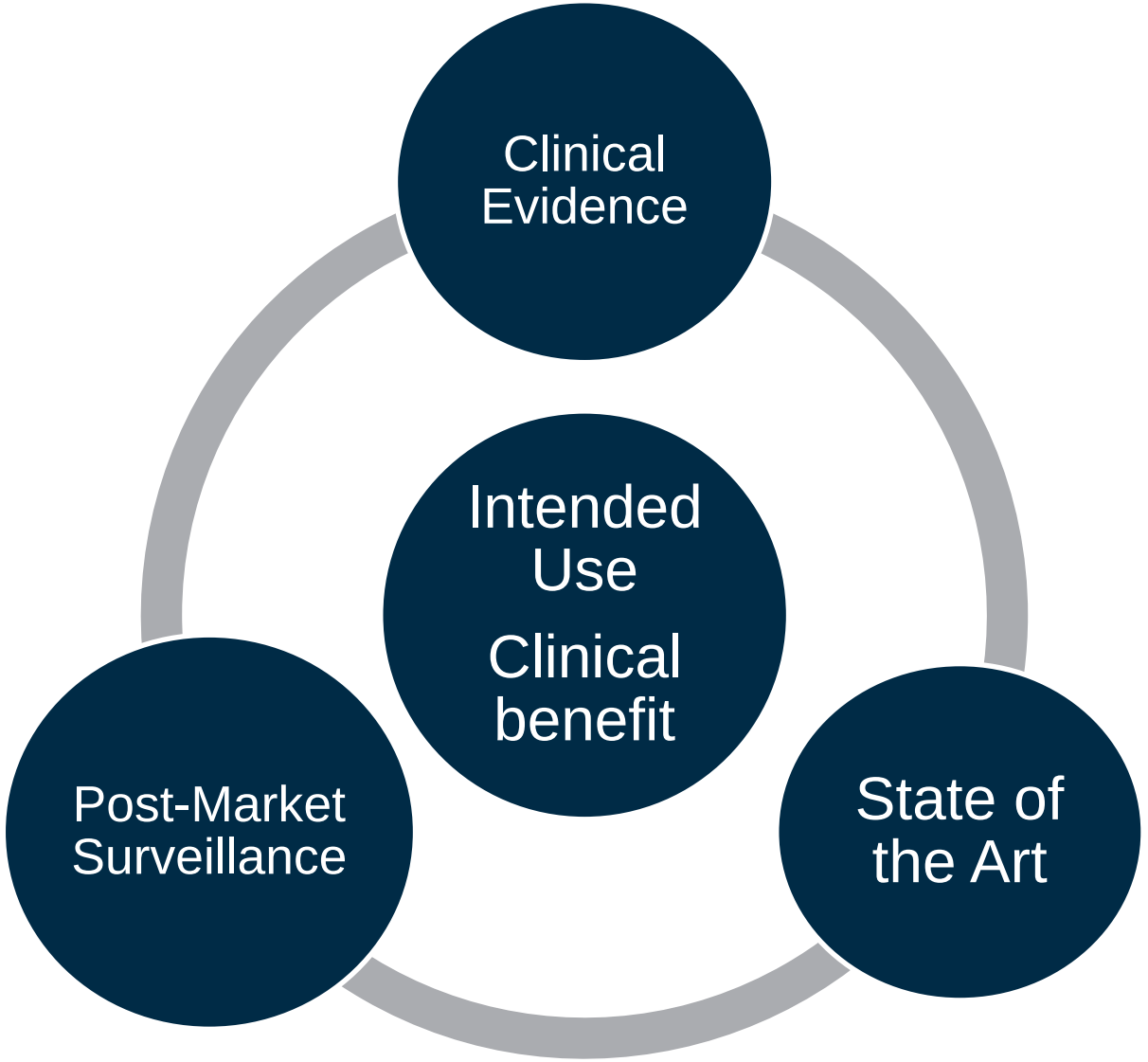
Clinical Evidence



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.**

…….

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**:**

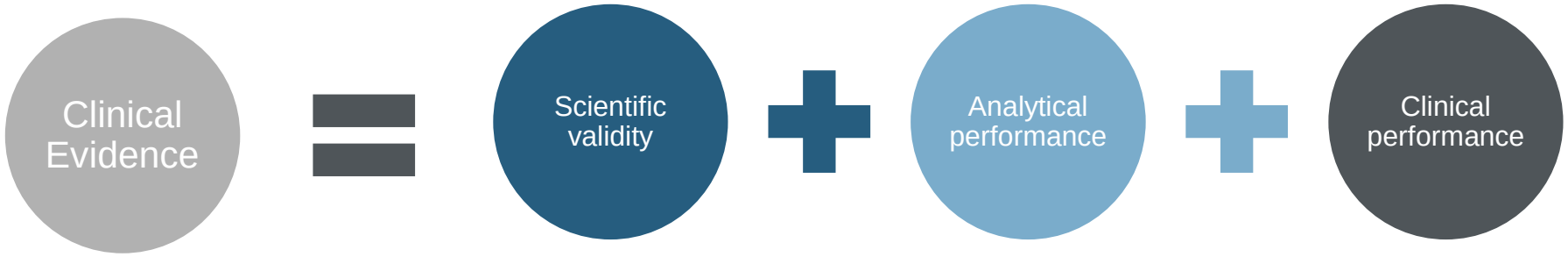
an identification of existing relevant standards, CS, Guidance, or best practices documents

--> 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

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**



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;

Agenda

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2	Overview (incl. transition period, general aspects)
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8	Post-Market Surveillance
9	Notified Body related aspects

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.

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

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

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

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 (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) ?

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

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

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 pro
  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) ?

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

Performance Evaluation

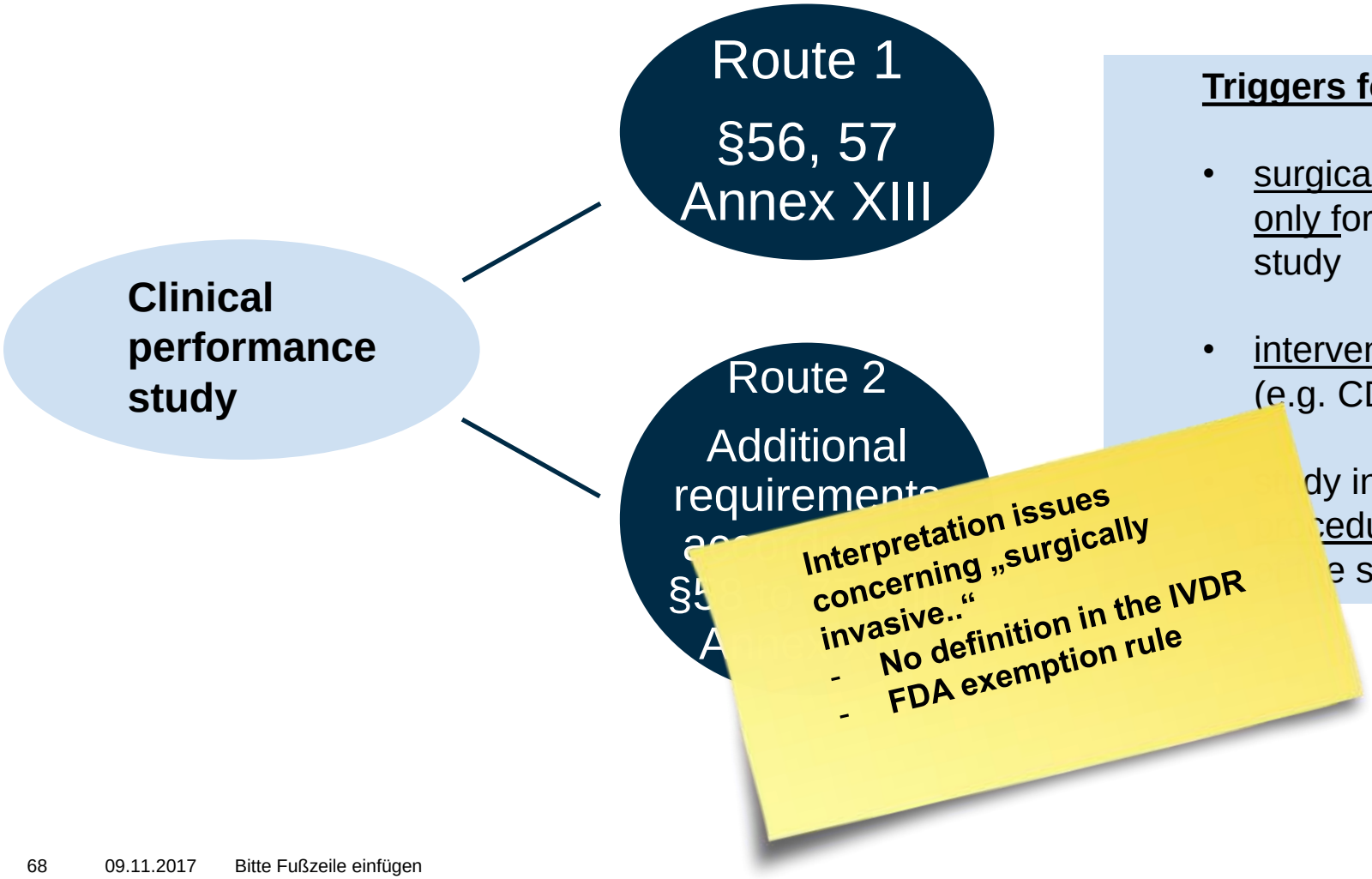
Deliverables defined in Annex XIII, Part A:

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

Performance Evaluation

Clinical performance study

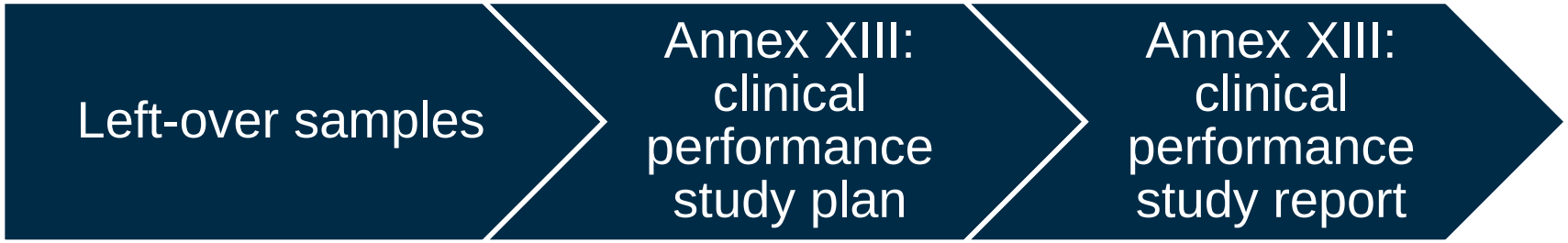


Triggers for additional route 2:

- surgically invasive sample-taking is done only for the purpose of the performance study
- interventional clinical performance study (e.g. CDx)
- dy involves additional invasive cedures or other risks for the subjects e studies

Performance Evaluation

Clinical performance study – Article 56/57 / Annex XIII



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 ?

Performance Evaluation

Clinical performance study

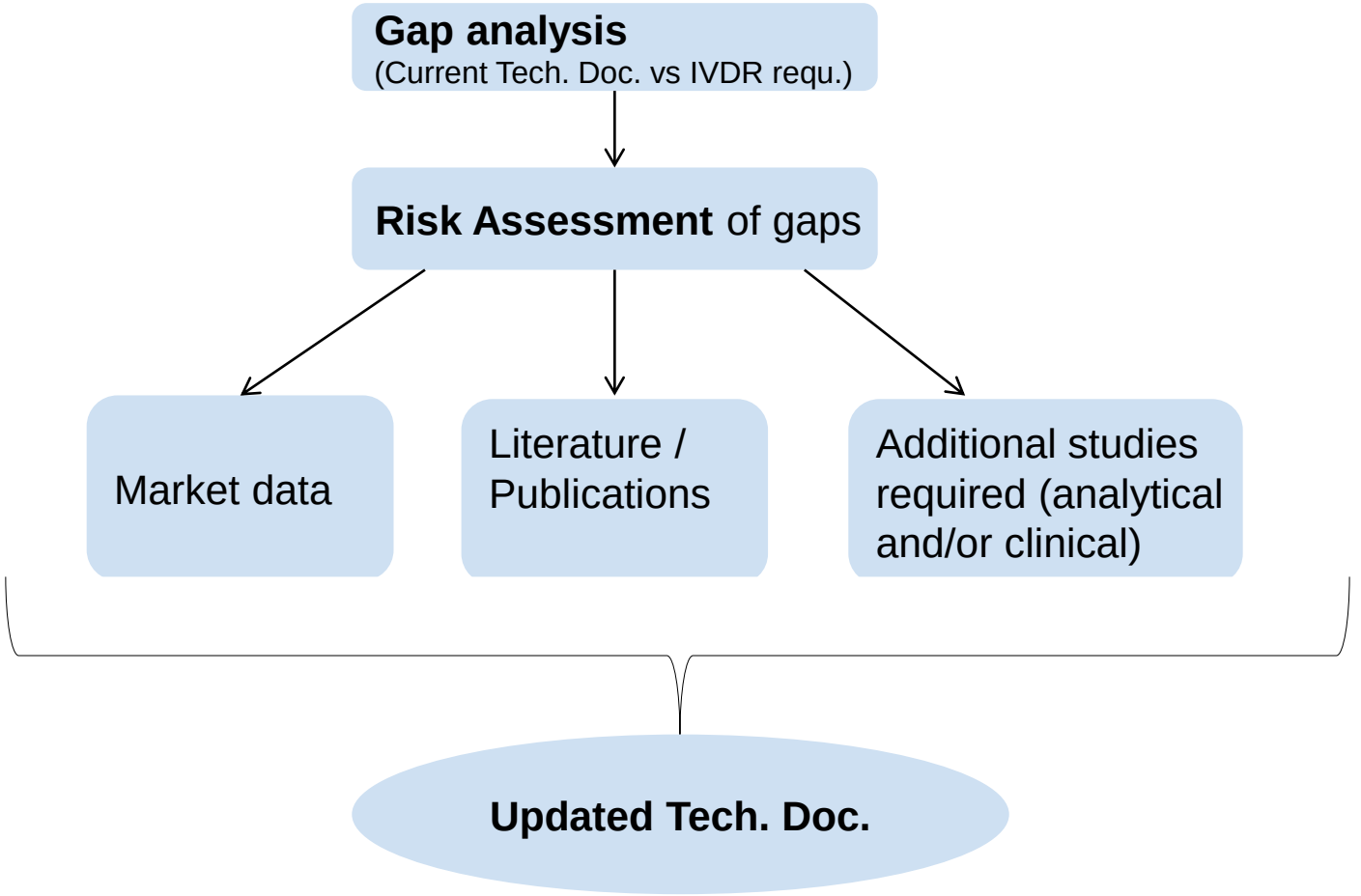
Clinical performance study report:

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



Agenda

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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**

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

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

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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Notified Body related aspects

NBOG Codes – NB Designation + TD sampling (current Draft)

Multi-dimensional system:

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

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

Notified Body related aspects

NBOG Codes – NB Designation + TD sampling (current Draft)

(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**
	intended to be used for pre-natal screening of women in order to determine une status towards transmissible agents
	tended to be used to detect the presence of, or exposure to transmissible lood, blood components, cells, tissues or organs, or in any of their to assess their suitability for transfusion, transplantation or cell n
	ntended 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

NBOG WD 2017-3 Draft Page 2 of 6

Competence requirements for NB

„Generic device groups“ - Sampling Class C ??

Notified Body related aspects

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

Notified Body related aspects

NBOG Codes – „IVD specifics“

(1) Specifics of in vitro diagnostic medical devices

IVS CODE	IVDR specifics
	evices intended to be used for near-patient testing
	vices intended to be used for self-testing
	ices intended to be used as companion diagnostics
	ces utilizing material of human origin
	s in sterile condition
	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

Additional competence requirements for NB

No grouping / sampling purpose ?

TÜVRheinland®
Genau. Richtig.

Notified Body related aspects

NBOG Codes – Types of examination procedures

Additional competence requirements for NB

„Product categories“ - Sampling Class B ??

(3) Types of examination procedures – product verification

IVDP CODE	IVDR types of examination procedures
IVP 3001	Agglutination tests
3002	Biochemistry
3003	Chromatography
004	Chromosomal analysis
05	Coagulometry
6	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

Notified Body related aspects

NBOG Codes – „Laboratory and clinical disciplines“

(4) Laboratory and clinical disciplines - product verification

IVDD CODE	IVDR laboratory and clinical disciplines
IVD 4100	Bacteriology
IVD 4101	- Multi-drug-resistant *mycobacterium* species (tuberculosis)
IVD 4102	- *Vibrio cholerae* (cholera)
IVD 4103	- Multi-resistant *Staphylococcus aureus* (and / or tests for resistance genes)
IVD 4104	- *Treponema pallidum* (syphilis)
IVD 4200	Clinical chemistry / biochemistry
IVD 4300	Detection of transmissible agents (without organisms or viruses)
IVD 4301	- Prion (Creutzfeldt-Jakob disease (CJD) and variant CJD (vCJD))
IVD 4400	Genetics

Purpose totally unclear

Clinical expertise of NBs ?
Designation of reference labs ?
Sampling (main groups) ?

IVD 4500	Haematology / haemostasis, including coagulation disorders‘
IVD 4600	Histocompatability and immunogenetics
IVD 4700	Immunohistochemistry / histology
IVD 4800	Immunology
IVD 4900	Molecular biology / diagnostics
IVD 5000	Mycology
IVD 5100	Parasitology
IVD 5101	- *Plasmodium* species (malaria)
IVD 5102	- *Toxoplasma gondii* (toxoplasmosis)
IVD 5103	- *Trypanosoma cruzi* (Chagas disease)
IVD 5200	Virology
IVD 5201	- Cytomegalovirus (CMV IgG)
IVD 5202	- Epstein-Barr virus (EBV)
IVD 5203	- Hepatitis B, C, D, E
IVD 5204	- Highly virulent pandemic influenza
IVD 5205	- HIV 1 & 2 (HIV / AIDS)
IVD 5206	- Human T-lymphotropic virus (HTLV)
IVD 5207	- SARS - coronavirus (SARS)
IVD 5208	- Lassa fever virus, Ebola virus, Marburg virus (viral haemorrhagic fevers)
IVD 5209	- West Nile virus (West Nile fever)
IVD 5210	- Zika virus (Zika fever)

Notified Body related aspects

Impact and strategies

Significant increase of resources by continued recruiting of new auditors and experts

expansion by 300% planned within the next 5 years at TÜV Rheinland

Establishing of new competencies, e.g.

Strategic project „Companion Diagnostics“ started

Recruiting / contracting of (clinical) experts for product groups currently not in the scope of NB conformity assessments (e.g. cancer marker, hemostasis etc)

Notified Body related aspects

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: 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

Conclusion

Potential actions to be taken by manufacturers:

First steps:

- Classification of the product portfolio
- „Gap“ analysis of existing Technical Documentations
- Strategic selection of Notified Body

Once the sampling approach is defined by the EU commision:

- draft a sampling plan to estimate the number of TF reviews required in a given cycle
- Mutual agreement concerning legacy products (missing DHF content, missing performance evaluation data)
- „voluntary“ submission of selected TF(s) for review against IVDR requirements

Once finalization of designation process is forseeable:

- Definition of sampling plan and agreement of transition plan to make use of the remaining transition period

Thank you very much for your attention!

Any further questions ?

Sven Hoffmann

Manager IVD
Global Head of Technical Competence Center IVD

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