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"IVDR compliant use of LDTs in the laboratory".

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Parlamentum Europaeum

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IVDD

EU Directive 98/79/EC

National Laws

Implementation

IVDR

Regulation (EU) 2017/746

Implementation

What do I want to talk about?

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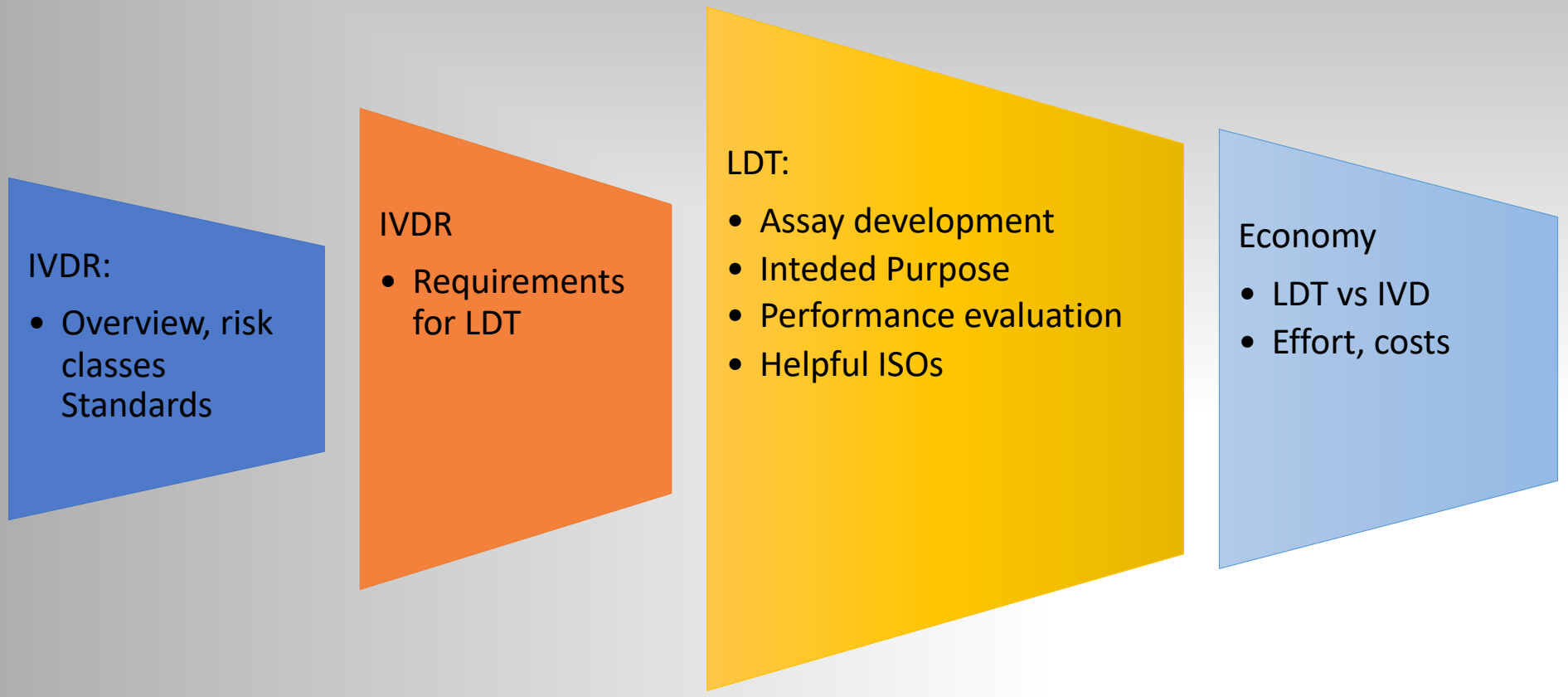

Definition of risk class under IVDD and IVDR

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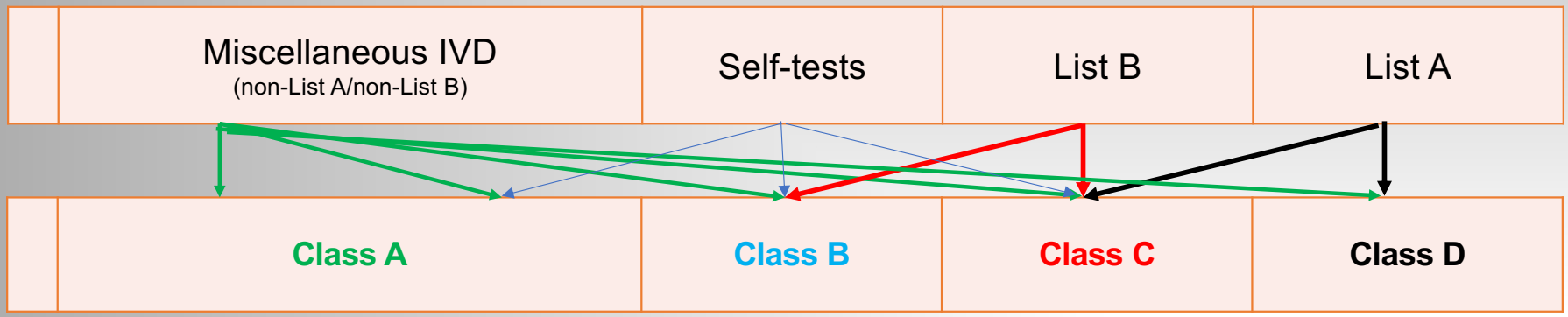
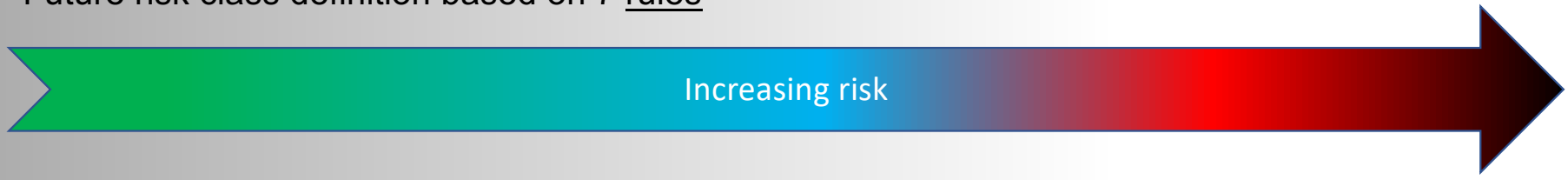
IVDD:
Currently valid list-based risk class definition



IVDR:
Future risk class definition based on 7 rules



IVDR: Overview, risk classes Standards

Basic structure of the IVDR

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10 chapters (I-X) with a total of 113 articles and 15 annexes

- Relevant chapters for LDT are:
  - II: Provision and commissioning of products
    - Article 5 (5)
  - V: Classification and conformity assessment
  - VI: Clinical evidence, performance evaluation and performance studies
- Relevant Annexes for LDT
  - Annex I (and II, VII and VIII "light")

Source: https://de-mdr-ivdr.tuvsud.com/EU-Verordnung-In-vitro-Diagnostika.html

IVDR: Overview, risk classes Standards

The IVDR Annexes (I-XV) define the requirements in Europe

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I:
Basic safety and performance requirements

II, III:
Technical documentation

IV:
Declaration of conformity

V:
CE marking

VI:
Registration and UDI

VII:
Requirements for notified bodies

VIII:
Classification

IX:
Conformity assessment based on full quality assurance or design examination

X:
Conformity assessment on the basis of a type examination

XI:
Conformity assessment based on production QA

XII:
Content of the certificate of the notified bodies

XIII, XIV:
Clinical Evidence and Post Market Follow-up

XV:
Correlation table

Red marked: LDT relevant

IVDR: Overview, risk classes Standards

Existing and future LDT requirements

Germany

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IVDD (MPG/MPBetreibV)	IVDR
Basic requirements according to IVDD Annex I (see MPG § 12 (1))	Basic safety and performance requirements according to IVDR Annex I
MPG $ 3 (22): IVDs from own production may not be manufactured on an industrial scale and may not be placed on the market.	LDTs may not be transferred to other legally independent facilities and are not part of the be produced on an industrial scale.
Classification according to IVDD Annex II and Conformity assessment procedure according to IVDD Article 9 and verb. Requirements (see MPG § 12 (1))	Classification according to IVDR Annex VIII (see Article 5 (5) g) and h))
Performance evaluation (see MPG § 19 (2); IVDD Annex I A. 3.)	Performance evaluation Article 56 (see Article 5 (3))
QM system according to Part A of the Rili-BÄK (see MPBetreibV § 9)	QM system according to EN ISO 15189 and, if applicable, chapters on production (see Article 5 (5) b) and c)).
MPV $ 5 (6): Conformity assessment procedure: Declaration of compliance with Annex | of the IVDD; incl. information on the health care facility and Identification of the products	Conformity assessment procedure: Publicly available declaration of the Compliance with Annex | (IVDR), incl. information on the Health facility and product identification
MPV § 5 (6): Product monitoring incl. corrective measures	Product monitoring incl. corrective measures

The IVDR does not apply to:

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1. Products intended only for law enforcement, or other non-medical purposes, (paternity tests drug/alcohol abuse tests)
2. Products for general laboratory use, or products intended solely for research purposes
3. Materials used for external quality assessment programmes (interlaboratory comparisons).
4. Internationally certified reference materials (e.g. standards for fluorescence, GC/MS)

IVDR: Overview, risk classes Standards

Who monitors compliance with the IVDR?

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Compliance with the IVDR (Article 5 (5) sentences 3, 4)

- **The state authorities** monitor laboratories for compliance with the IVDR and the MPBetreibV/ RiliBÄK.
- **DAkkS** verifies if your laboratory is ISO 15189 accredited.

IVDR: Overview, risk classes Standards

Standards and guidelines

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Standards help to make products and solutions comparable

ISO 15189:
Requirements for a quality management system for medical laboratories.

ISO 13485:
Requirements for the development, implementation and maintenance of management systems and the design and manufacture of medical devices

ISO 20916:2019
Requirements for planning and conducting clinical performance studies.

Guidance documents essentially explain how the IVDR requirements are implemented in detail.

MDCG 2022-2:
Guideline on the general principles of clinical evidence for in vitro diagnostic medical devices (IVDs)

MDCG 2021-24:
Guideline on the classification of medical devices

- DIN : German industrial standard
- EN: European standard
- ISO: Standard of the International Standard Organisation
- MDCG: Medical Device Coordination Group

IVDR: Overview, risk classes Standards

Certification, Accreditation, RiliBÄK

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Certification
Lat: certus: "determined

Procedure by a body or organisation to obtain evidence of compliance with certain requirements

Accreditation
Lat: accredere: "to give credence to".
Confirmation and recognition of professional competence.

The Rili-BÄK
sets minimum requirements for all operators and users of in vitro diagnostic medical devices (laboratories and their staff)

IVDR: Overview, risk classes Standards

Basic structure of DIN EN ISO 15189

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Technical requirements	Management requirements	QMS Basics
Laboratory equipment, reagents and consumables	Management organisation and accountability	Organisation
Pre-analytical measures Examination procedure	Quality management system	Customer orientation
Ensuring the quality of the examination results	Steering of documents	Facilities and security
Postanalytical measures	Service agreements	Staff
Reports on findings	Investigation by contract laboratories	Purchasing and Materials Management
Release of the results	External services and supplies	Resources
Information management of the laboratory	Counselling services Clarification of complaints	Process management
Staff	Detection and processing of errors	Documents and records
Premises and environmental conditions	Corrective measures	Information management
	Preventive measures	Non-compliance event
	Constant improvement	Management
	Control of records	Assessments
	Assessment and audits	Constant improvement
	Management assessment	
Source: International Organization for Standardization (ISO) 15189. Schneider et al. Ann Lab Med. 2017 Sep		

IVDR: Overview, risk classes Standards

New regulation of the IVDR

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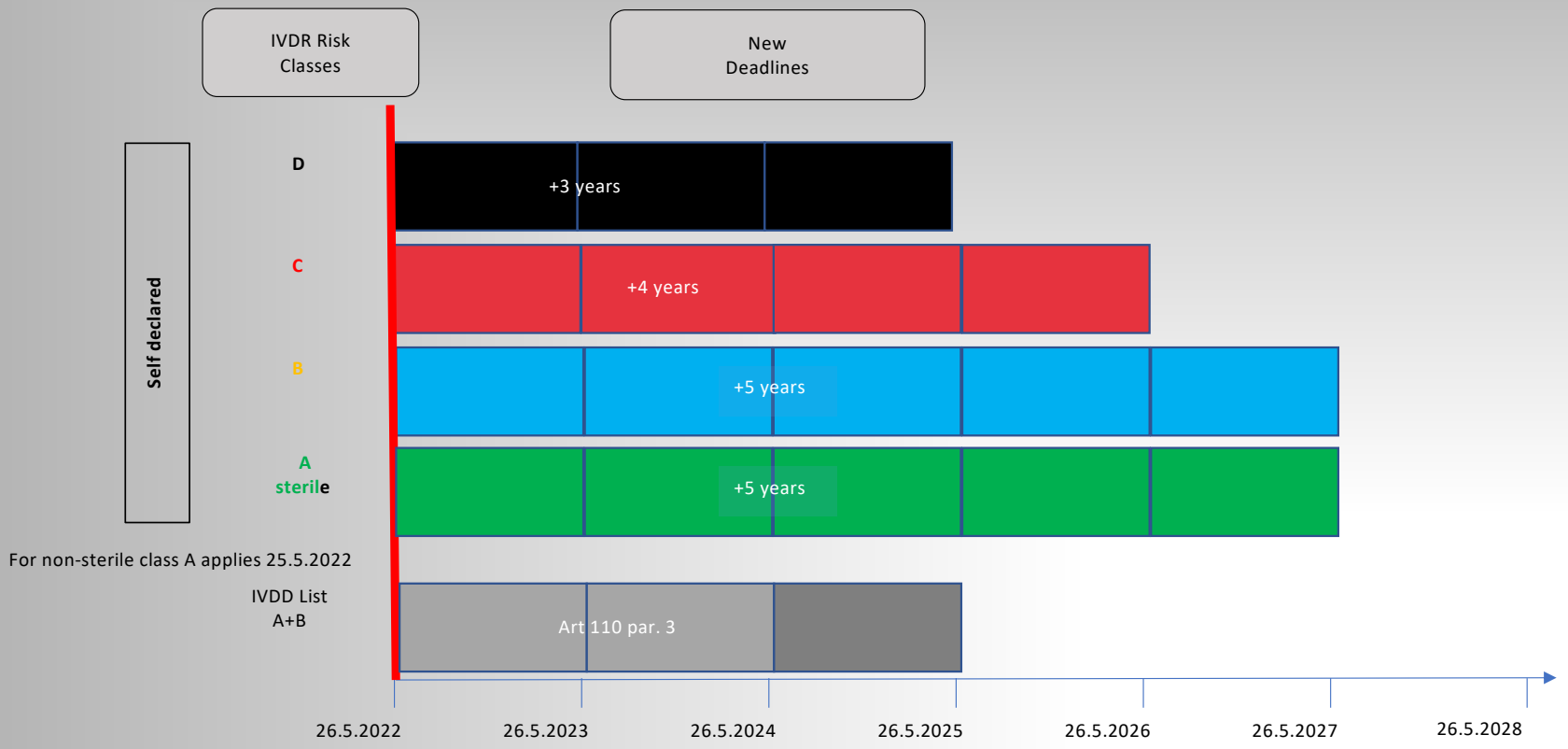

New provision Art 5 (5)

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a) Passing on LDTs

Quality management system	(b) the manufacture and use of the products take place within the framework of appropriate quality management systems
Quality assurance in the laboratory	(c) the laboratory of the health care establishment complies with standard EN ISO 15189 or, where applicable, with national provisions, including national provisions on accreditation
No LDT in case of similarity of a commercial product	😀
Information to authorities	(e) the health care facility makes available to its competent authority, on request, information on the use of such devices that provides a rationale for their manufacture....
public train. Declaration	(f) the health facility prepares a statement which it makes publicly available .....
Documentation	(g) for class D devices in accordance with the provisions of Annex VIII, the health care establishment shall draw up documentation, ... Member States may also apply this provision to class A, B or C devices in accordance with the provisions of Annex VIII
Proof of manufacture	(h) the healthcare establishment takes all necessary measures to ensure that all devices are manufactured in accordance with the documentation referred to in point (g)
Serious incidents and corrective actions	(i) the healthcare facility shall review the experience of clinical use of the devices and take any necessary corrective action.

26.5.2022 26.5.2023 26.5.2024 26.5.2025 26.5.2026 26.5.2027 26.5.2028

https://www.johner-institut.de/blog/johner-institut/uebergangsfristen-der-ivdr/

IVDR requirements for LDTs

What are LDTs ?
(Homebrew, own development)

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1. In-house procedure
   - Procedure developed in the laboratory with equipment, reagents, controls etc. without CE marking (e.g. PCR device with Fischer technique, self-synthesised primers, self-purified Taq polymerase).
2. Research Use Only (RUO)
   - Use of RUO products for *in vitro diagnostic* purposes
3. CE/RUO Mix
   - Combination of CE-marked and RUO-marked products into a "stand-alone" system for in vitro diagnostic purposes
4. Off-Label Use
   - Use of CE-IVD tests outside of those described in the manufacturer's IFU.

IVDR requirements for LDTs

Requirements for IVDR compliant LDT

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Necessary:

Quality management

- ISO 15189 RILIBÄK

Necessary:

Risk Management system

- ISO 14971, 22367

Helpful:

Technical documentation

- Evidence of compliance with Annex I

Helpful:

Conformity-declaration

- Proof of compliance with Annex I

Necessary:

Documented assessment of the experience

- Review of tests, CAPA* according to ISO 15189

*Corrective and Preventive Action

IVDR requirements for LDTs

Risk management

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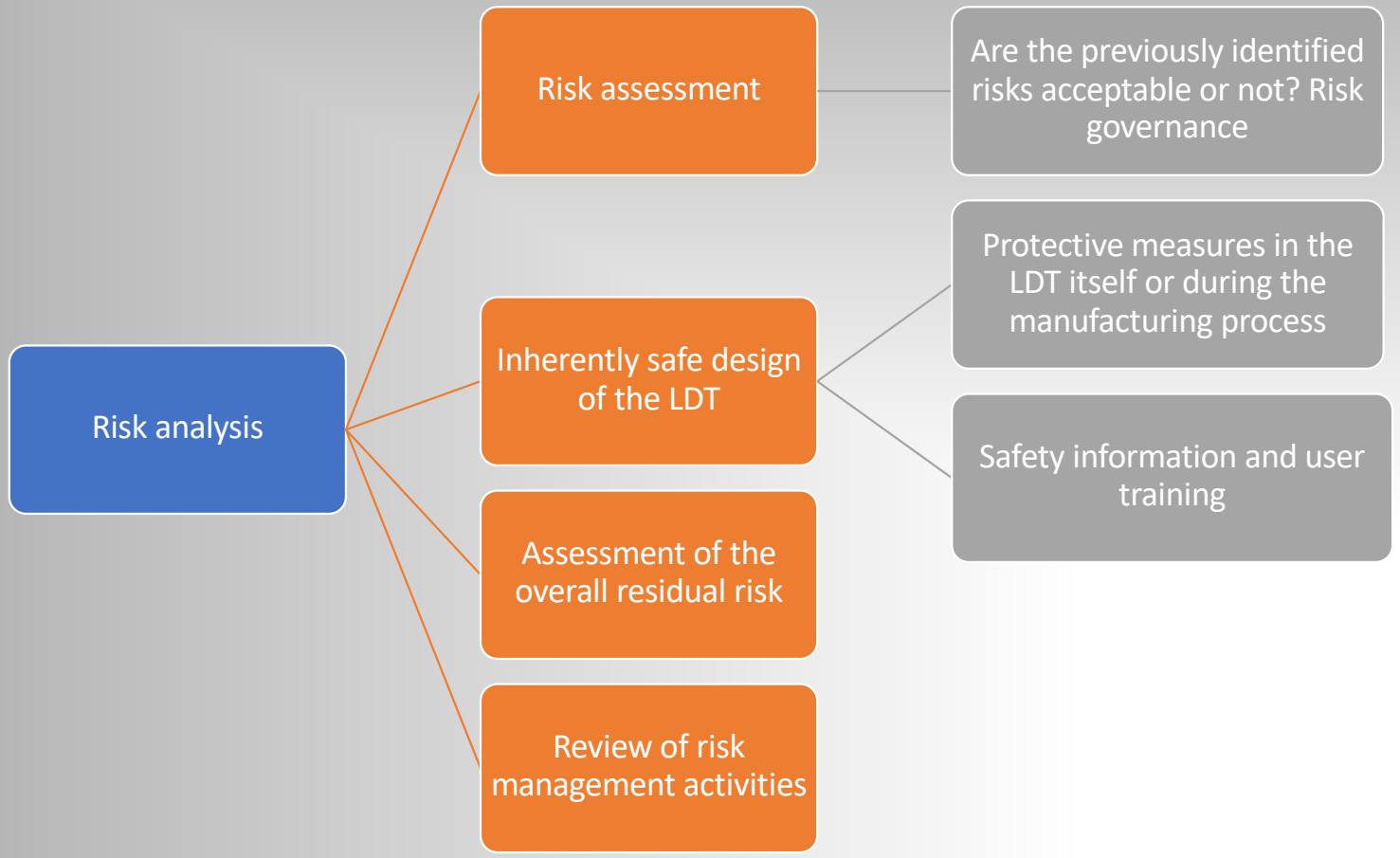

LDT:

- Assay development
- Purpose
- Performance evaluation

How to make an LDT IVDR compliant

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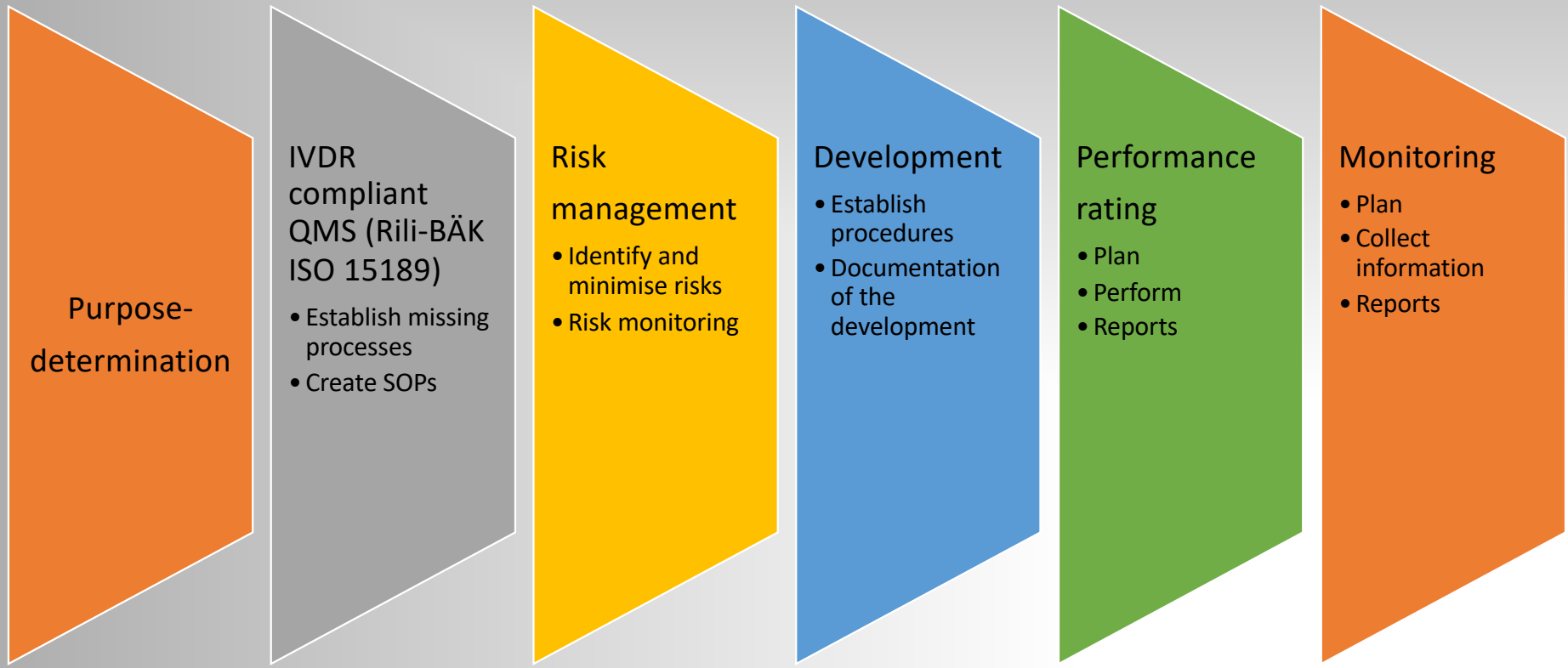

LDT:
- Assay development
- Purpose
- Performance evaluation

Intended Purpose Requirements

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- The intended use specifies the use of the LDT and is composed of:
  - **medical purpose:**
    - Which disease should be tested?
  - **medical application:**
    - Who applies it, who should be tested?
  - **intended use:**
    - How is the test applied (if applicable, which devices are necessary for this)?

LDT:

- Assay development
- Purpose
- Performance evaluation

An LDT is usually part of an IVD process

e.g. analysis by a PCR assay

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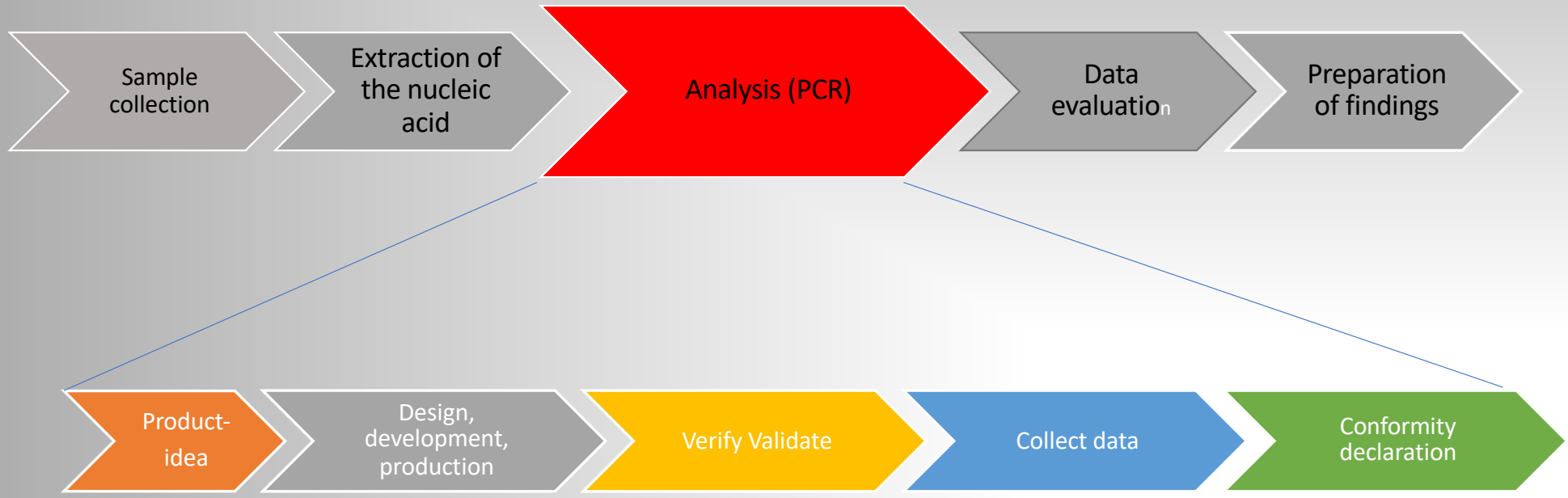

Components of an LDT development

LDT:

- Assay development
- Purpose
- Performance evaluation

Basic steps of LDT development

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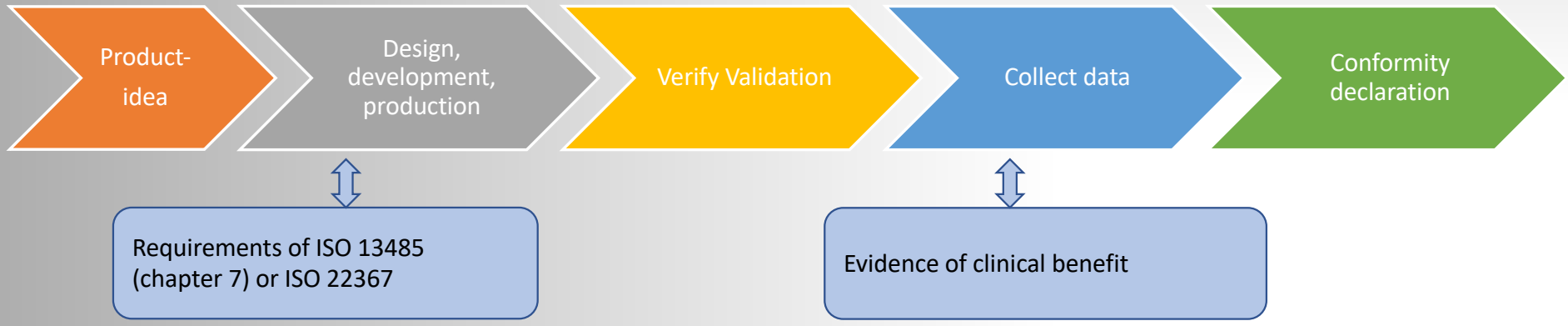
RiliBÄK and ISO 15189 do not contain any requirements for the development and manufacture of in vitro diagnostic products.
ISO 22367 (risk management standard) describes the approach to design and development activities related to LDTs such as development planning, results, governance of development changes, etc. (corresponds to chapter 7 of ISO 13485 standard).



LDT:

- Assay development
- Purpose
- Performance evaluation

Performance evaluation

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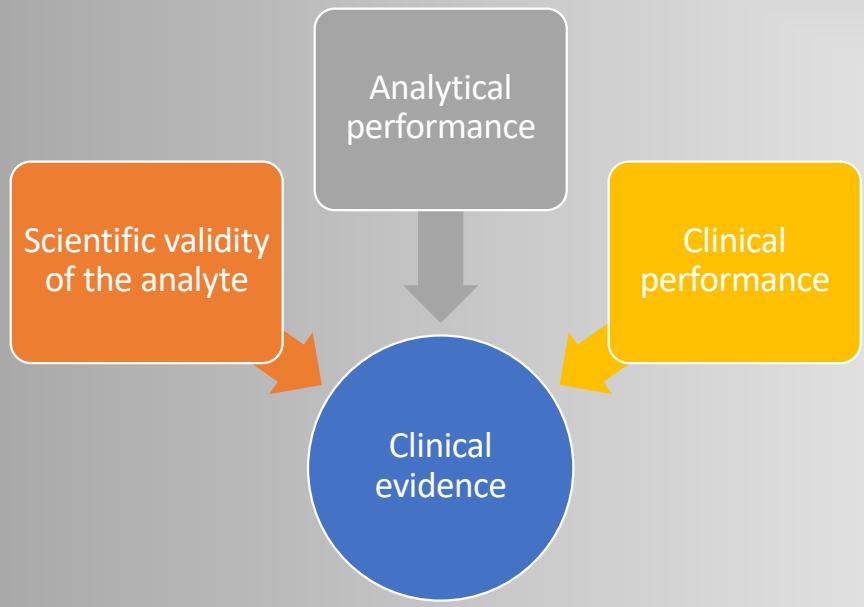
Evidence of clinical benefit underpins the intended purpose of the device and is based on an ongoing process of performance evaluation according to a performance evaluation plan



Evidence of clinical benefit is provided by:

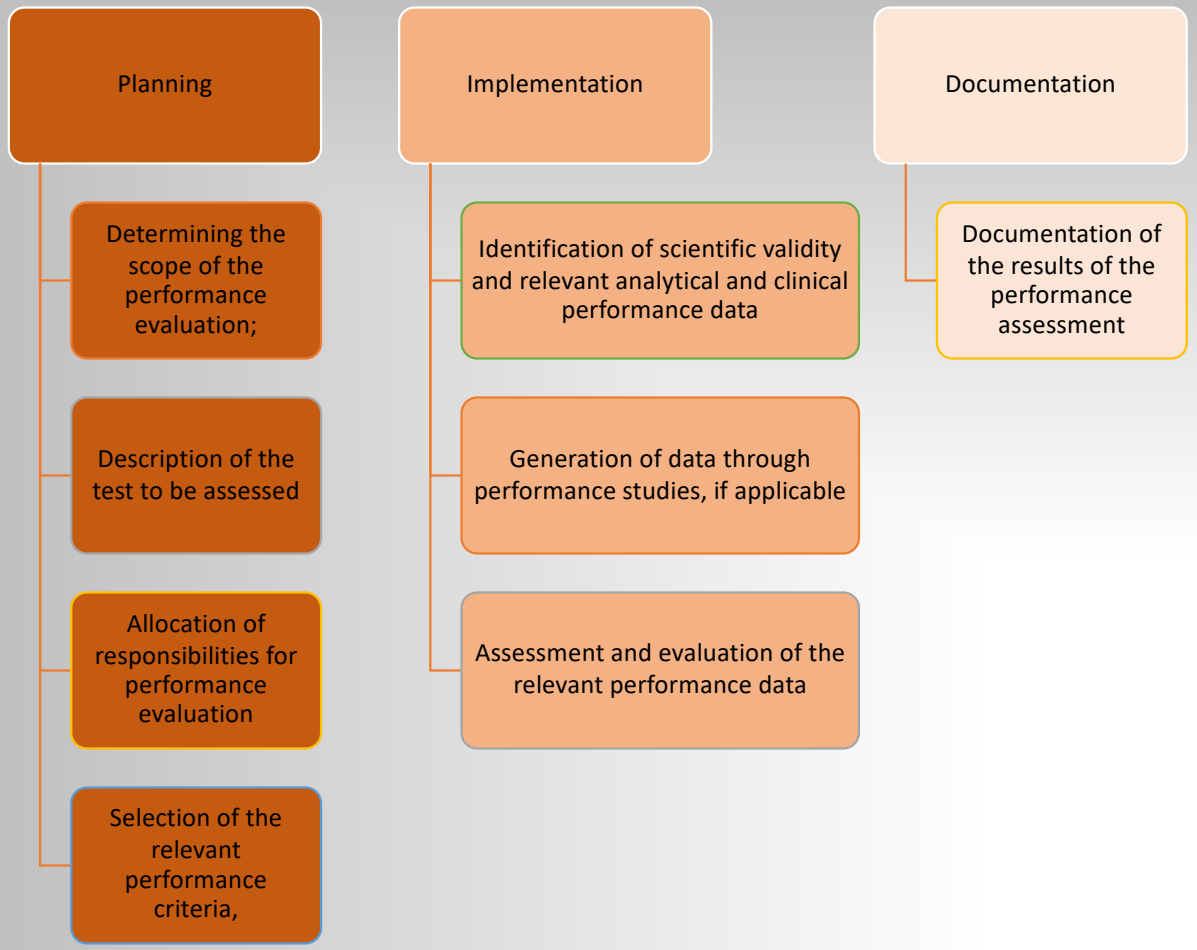
1. scientific validity
   Scientific Validity Report (SVR),
2. analytical performance
   Analytical Performance Report (APR)
3. Clinical performance
   Clinical Performance Report (CPR)

The scope of the evidence increases with the risk class.

LDT:

- Assay development
- Purpose
- Performance evaluation

Overview of an LDT performance assessment



LDT:

- Assay development
- Purpose
- Performance evaluation

Clinical performance

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Required parameters for determining clinical performance (Annex I, Section 9.1 b) :

- diagnostic sensitivity
- diagnostic specificity
- Positive predictive value (PPV)
- Negative predictive value (NPV)
- Likelihood ratio
- expected values in unaffected and affected populations.
- Proof

Evidence of the clinical performance of a device is based on **one** or a **combination of** the following sources:

- clinical performance studies,
- scientific literature that has been subjected to peer review,
- experience gained from routine diagnostic tests that have been published.

Performance studies are only avoidable if other sources are available (Annex XIII Part A Section 2)

LDT:

- Assay development
- Purpose
- Performance evaluation

Analytical performance

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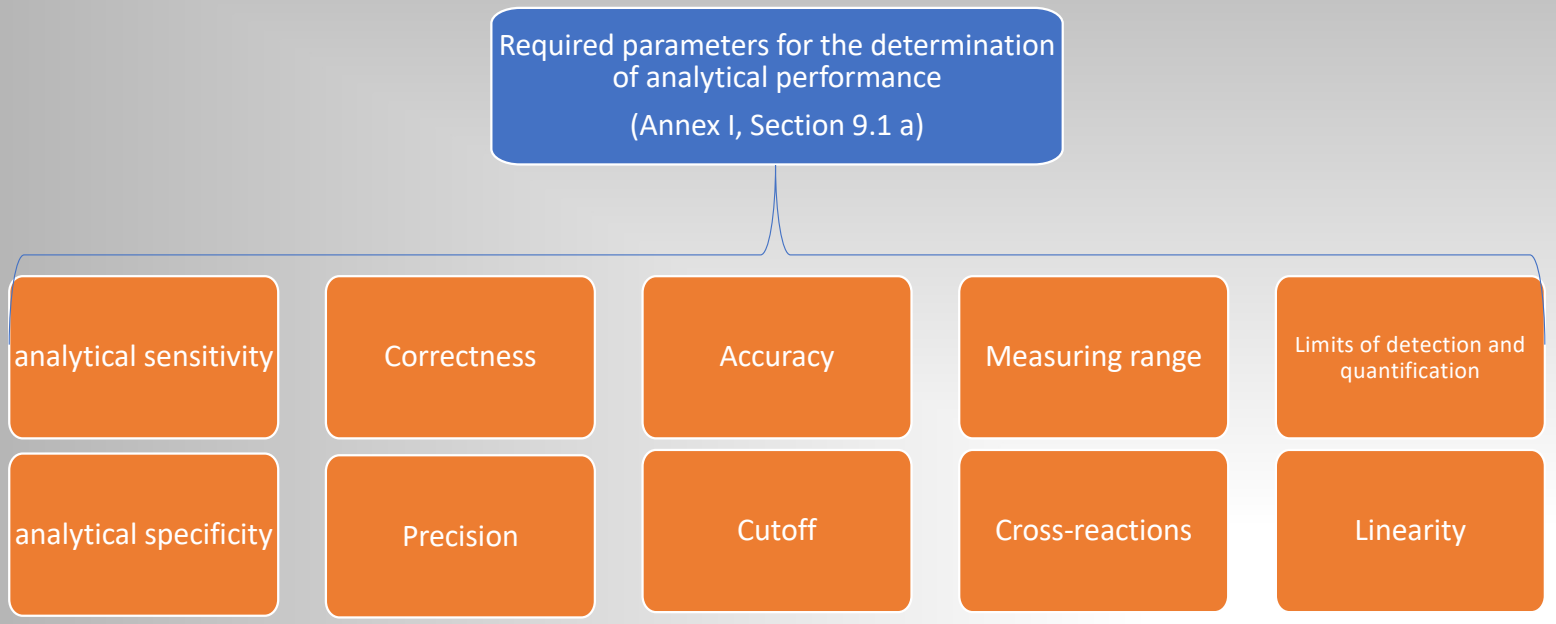

LDT:

- Assay development
- Purpose
- Performance evaluation

Scientific validity

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The relationship of the analyte to a specific clinical or physiological condition must be scientifically proven and documented

Evidence based on relevant data on the scientific validity of products measuring the same analyte or marker.

scientific literature (peer-reviewed)

Consensual expert opinion/opinion of relevant professional organisations

Results from studies to prove the principle of action

Results from clinical performance studies

Economy

LDT vs IVD

- Effort, costs

CE-IVD or LDT:
From the shelf or do-it-yourself?

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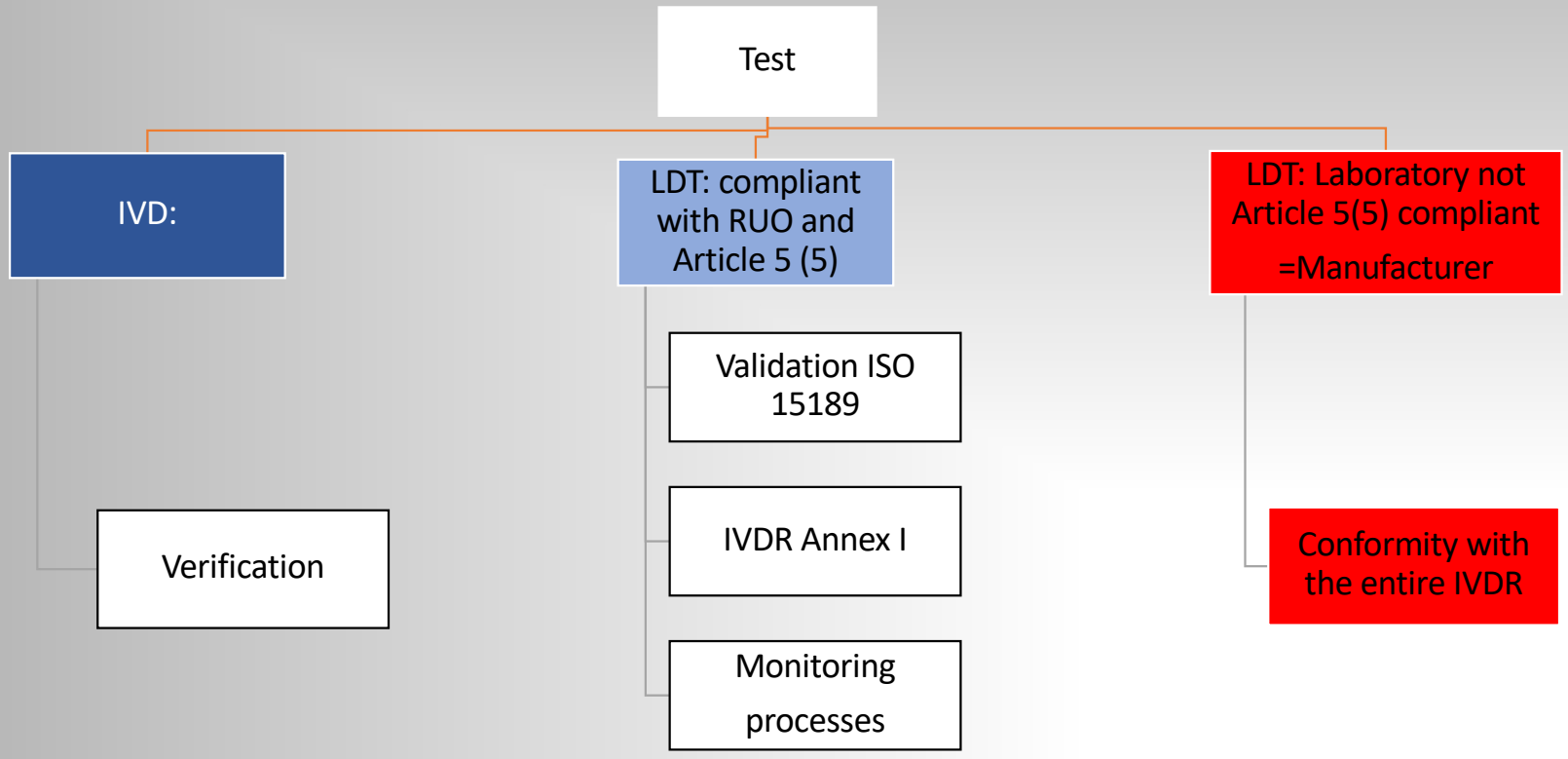
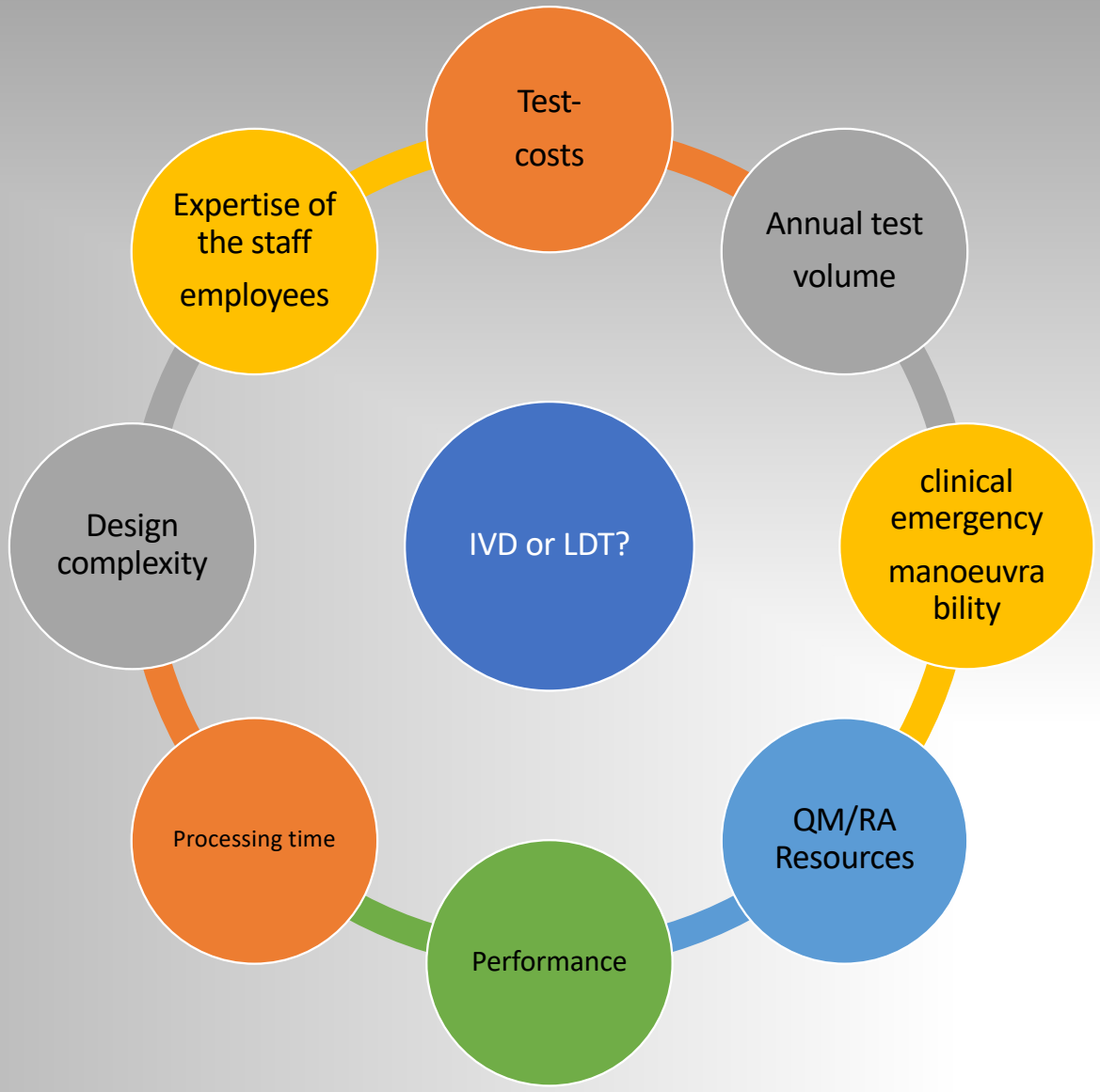


Economy

LDT vs IVD

- Effort, costs



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Summary

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The IVDR is not as burdensome for laboratories as is sometimes claimed

Basic requirements to be able to use own developments

1. Add specifications for manufacturing to the QMS
2. Meet the new requirements of the Rili-BÄK 2019.
3. Comply with the additional requirements of Article 5 (5) of the IVDR.
4. Comply with the extended requirements of Annex I of the IVDR.

Health care facilities that do not fulfil the requirements of Article 5 (5) by 26.5.2024 will be treated as IVD manufacturers, i.e.

- Mandate a Notified Body
- Establish processes for post-market surveillance