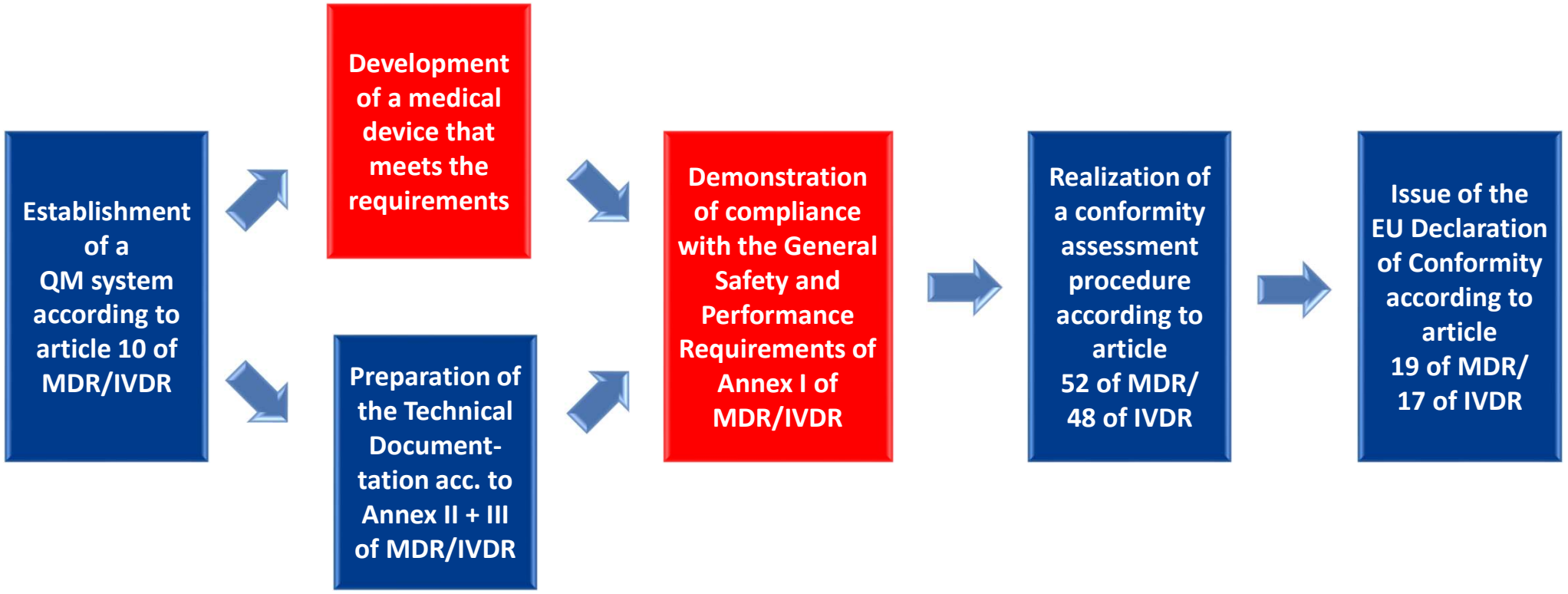
Risk based Approaches for Process Validation

Conformity Assessment for IVD-/Medical Devices

How do I get the CE mark for my product?



Regulatory sources

ISO 13485:2016

21 CFR 820.75 (a) [9.3]

MDR 2017/745

GHTF Quality Management Systems – Process Validation Guidance 2004

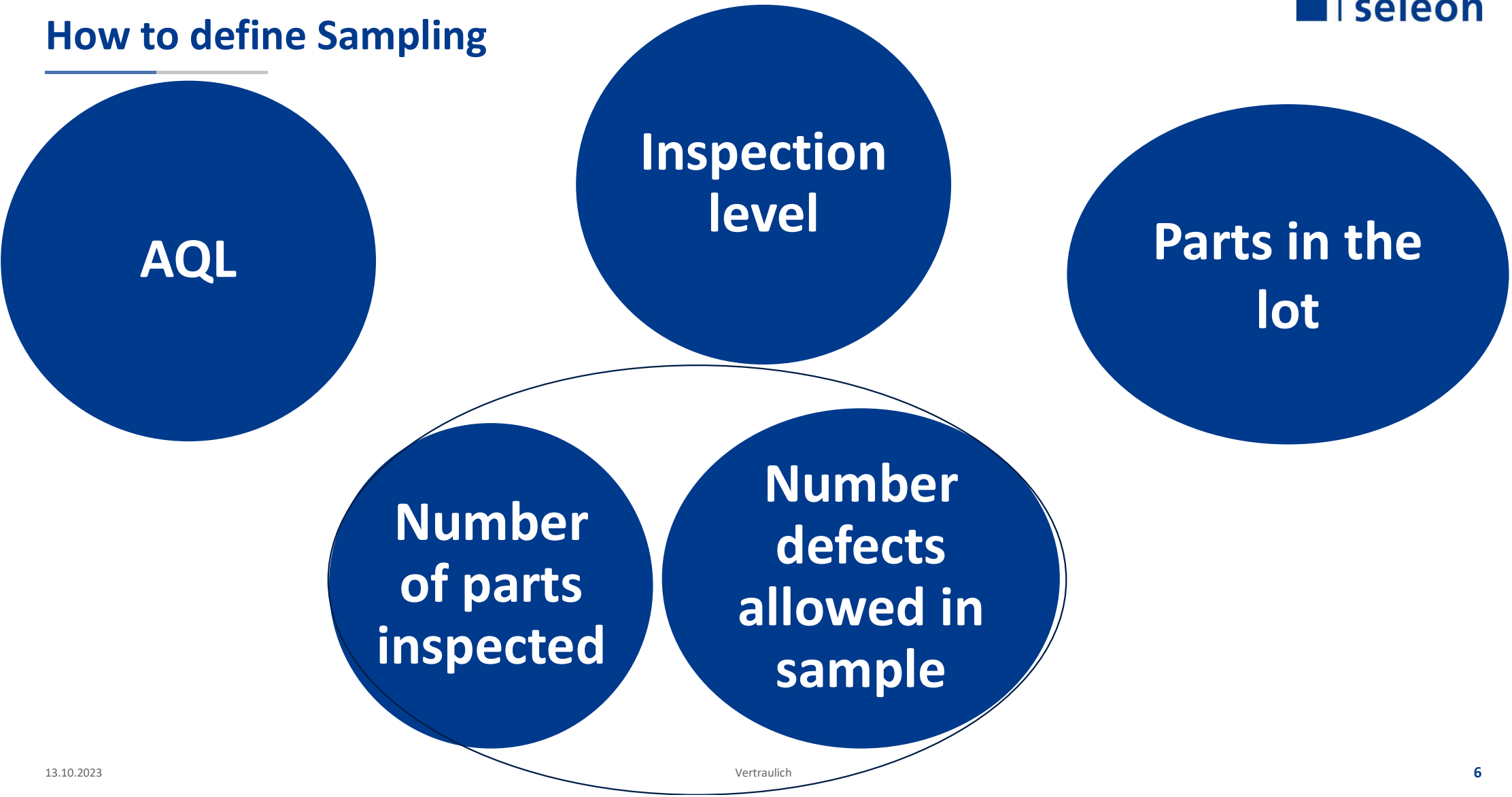
Steps to be taken before Process Validation

Term definition

Process validation:

establishing by **objective evidence** that a process consistently produces a result or product meeting its predetermined requirements.

How to define Sampling



Standards refering to AQL

DIN ISO 2859-1

Sampling procedures for inspection by attributes Part1: Sampling schemes indexed by acceptance quality limit (AQL) for lot by lot inspection

ISO 3951

Sampling procedures for inspection by variables –

Part 1: Specification for single sampling plans indexed by acceptance quality limit (AQL) for lot-by-lot inspection for a single quality characteristic and a single AQL

AQL method

Part I

1. Choose the LOT size
   Example: n = 410

2. Identify your Inspection Level: Criteria based on risk of component/ process step regarded
   Example: Level II (used in most cases. Good medium ratio between input and results)

3. Code letter identification
   Example: „H“

AQL-Auswahl der Kennbuchstaben
Qualitätive Stichprobenprüfung (zählende Prüfung) nach DIN/ISO 2859

2859

Losumfang	besondere Prüfniveaus				allgemeine Prüfniveaus		
	S - 1	S - 2	S - 3	S - 4	I	II	III
2 bis 8	A	A	A	A	A	A	B
9 bis 15	A	A	A	A	A	B	C
16 bis 25	A	A	B	B	B	C	D
26 bis 50	A	B	B	C	C	D	E
51 bis90	B	B	C	C	C	E	F
91 bis150	B	B	C	C	D	F	G
151 bis 280	B	C	D	E	E	G	H
281 bis 500	B	C	D	E	F	H	J
501 bis1200	C	C	E	F	G	J	K
1201 bis 3200	C	D	E	G	H	K	L
3201 bis 10000	C	D	F	G	J	L	M
10001 bis 35000	C	D	F	H	K	M	N
35 001 bis 150 000	D	E	G	I	L	N	P
150 001 bis 500 000	D	E	G	J	M	P	Q
500 001 und darüber	D	E	H	K	N	Q	R

AQL method

Part II

4. Identify sample size
   Example: for „H“ it is 50

5. Choose AQL level
   Example: 1 % (meaning: 1 % of a production run can be defective)

6. Read statistical test result
   Example: c: 1 and d: 2
   (meaning: accept production run, if ≤ 1 defects are found and reject if ≥ 2 defects are found)

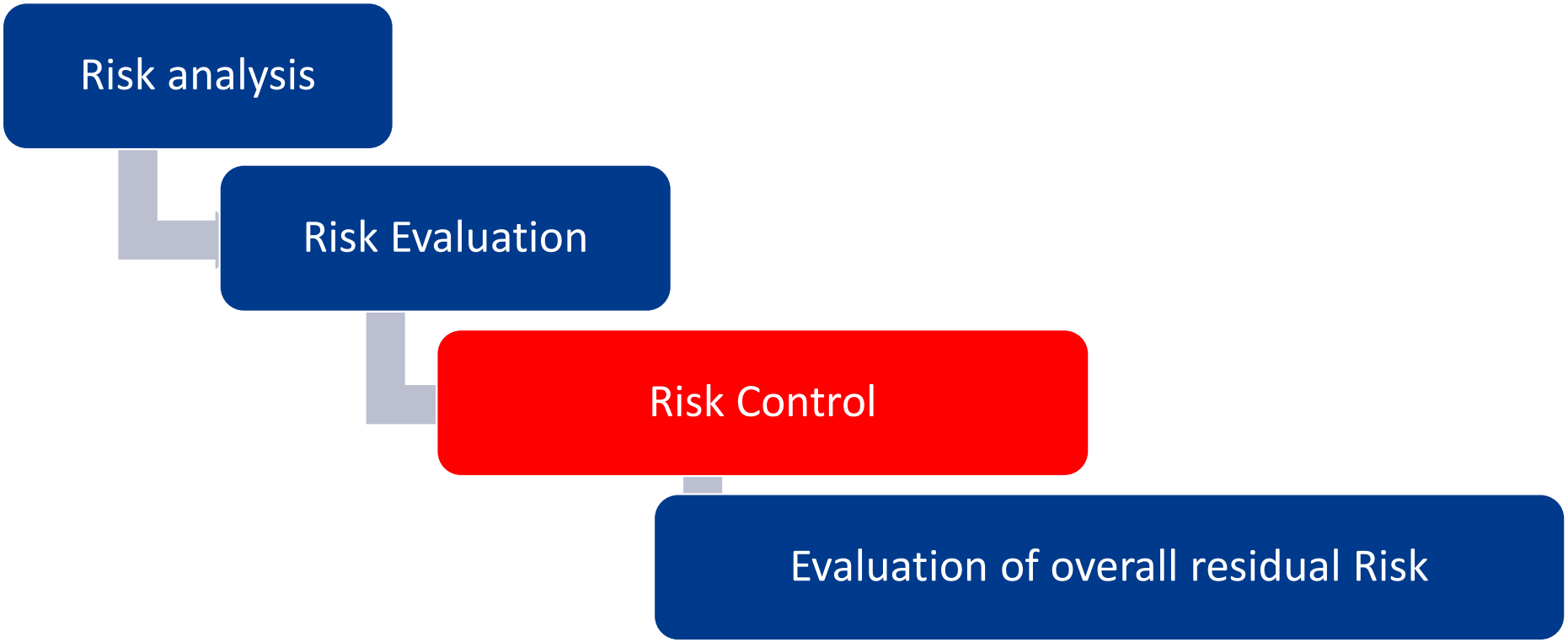
ISO 2859 einfach

Qualitative (zählende) Stichprobenprüfung, Einfachpläne, normale Prüfung
nach DIN/ISO 2859 (Auszug) frühere Norm DIN 40 080
AQL-Zahl -----> Kennbuchstabe -----> Stichpr.Anweisung n - c

Kennbuchstabe	Stichprobenumf. n	0,065	0,1	0,15	0,25	0,4	0,65	1	1,5	2,5	4	6,5	10	15	25	40
		c d	c d	c d	c d	c d	c d	c d	c d	c d	c d	c d	c d	c d	c d	c d
A	2											0 1			1 2	2 3
B	3										0 1			1 2	2 3	3 4
C	5									0 1			1 2	2 3	3 4	5 6
D	8								0 1		1 2	2 3	3 4	5 6	7 8	7 8
E	13							0 1		1 2	2 3	3 4	5 6	7 8	10 11	10 11
F	20						0 1		1 2	2 3	3 4	5 6	7 8	10 11	14 15	14 15
G	32					0 1			2 3	3 4	5 6	7 8	10 11	14 15	21 22	21 22
H	50				0 1			1 2	2 3	3 4	5 6	7 8	10 11	14 15	21 22	
J	80			0 1			1 2	2 3	3 4	5 6	7 8	10 11	14 15	21 22		
K	125		0 1			1 2	2 3	3 4	5 6	7 8	10 11	14 15	21 22			
L	200	0 1			1 2	2 3	3 4	5 6	7 8	10 11	14 15	21 22				
M	315			1 2	2 3	3 4	5 6	7 8	10 11	14 15	21 22					
N	500		1 2	2 3	3 4	5 6	7 8	10 11	14 15	21 22						
P	800	1 2	2 3	3 4	5 6	7 8	10 11	14 15	21 22							
Q	1250	2 3	3 4	5 6	7 8	10 11	14 15	21 22								
R	2000	3 4	5 6	7 8	10 11	14 15	21 22									

Risk Management

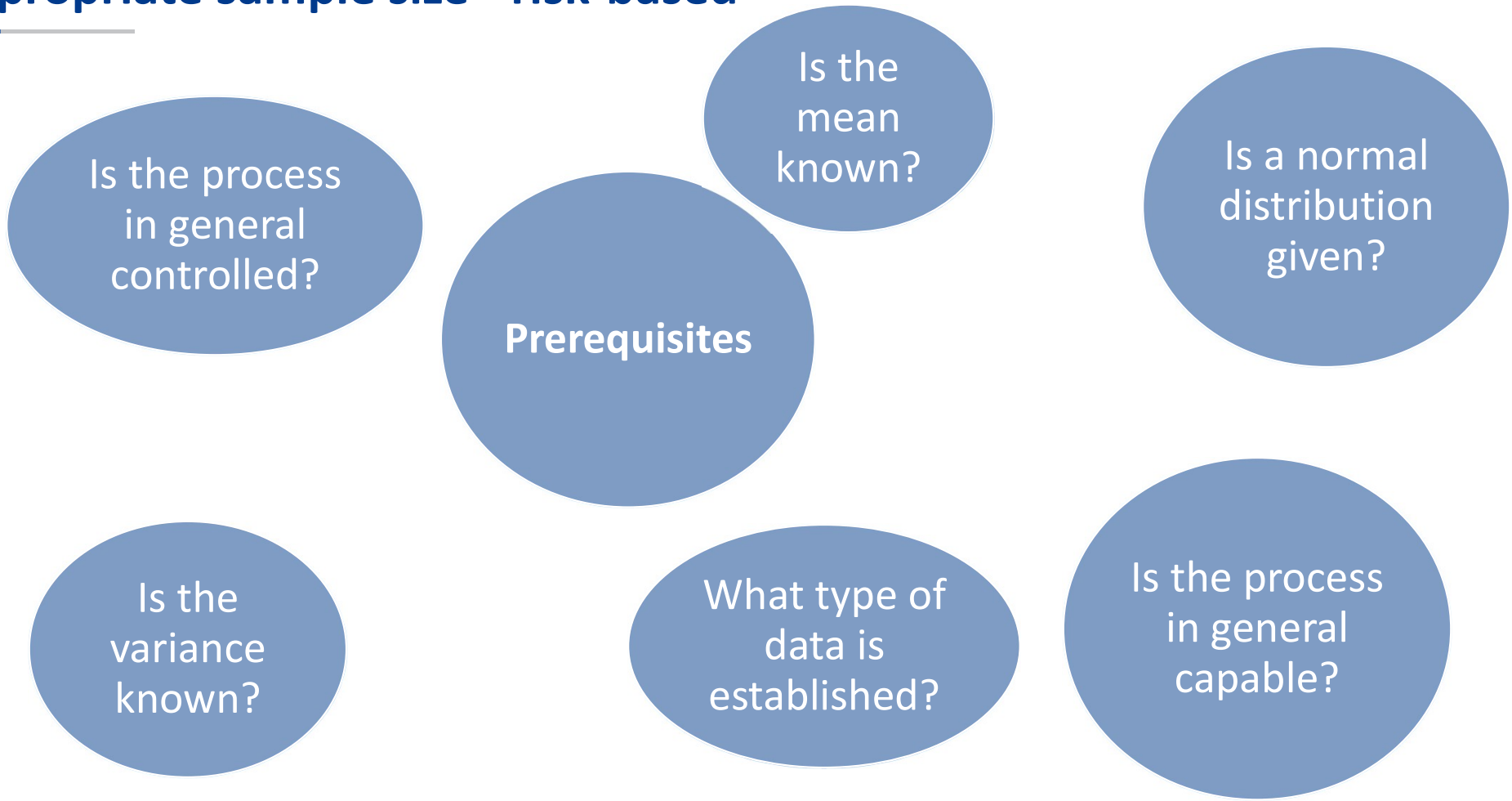
ISO 14971:2019



What does risk-based approach mean?

- Scaling of quality requirements in relation to the **risk to patients and users** associated with the error;
- The definition of the criteria in coordination with the company management and those responsible for **risk management**.
- High hazards or even high process risks entail **higher requirements** for the quality level of the products, which is associated with a higher testing effort.
- However, the definition of a quality level expresses the expectation that the process is reliably better than the defined quality level.
- As a further factor, the confidence level can be varied, i.e. the probability of the correctness of a statement. A confidence level of 95% is common.

An appropriate sample size - risk-based



Example statistical approach - medical device

Hazard	Sequence of events	Hazardous situation	Harm	Probability	Severity	Initial Risk	Measure	Implementation Reference	Effectiveness of RCM
Information hazards	required markings on the ME EQUIPMENT are not readable or missing. Therefore user mixes up product numbers or OPERATOR has got no information about device, reprocessing, procedures, etc	User cannot assign information provided in the ACCOMPANYING DOCUMENTS to the product and misinterprets reprocessing requirements	Serious infection that can be treated medicinally	P-2	S-4	S4-P2	Process validation black lase… m…	Device Requir… l… …on …vice	…erification Report

How many test samples are required?

Example Statistical Approach - Medical Device

Success Run Theorem

- For no-error sampling plans, the following applies:

$$n = \frac{\ln(1 - Confidence)}{\ln(Reliability)}$$

- Reliability- und Confidence level according to Risk assessment

Risk Control Measures – Verification & Validation					
Severity of Harm	Negligible (S-1) Notice	Minor (S-2) Caution	Serious (S-3) Caution	Critical (S-4) Warning	Catastrophic (S-5) Danger
Reliability level	90%	90%	95%	95%	99%
Confidence level	75%	75%	75%	95%	95%
n	14	14	27	59	298

RL = 0.95
CL = 0.95

→Is there any possibility to reduce the number of test samples?

Example statistical approach - medical device

Requirement:

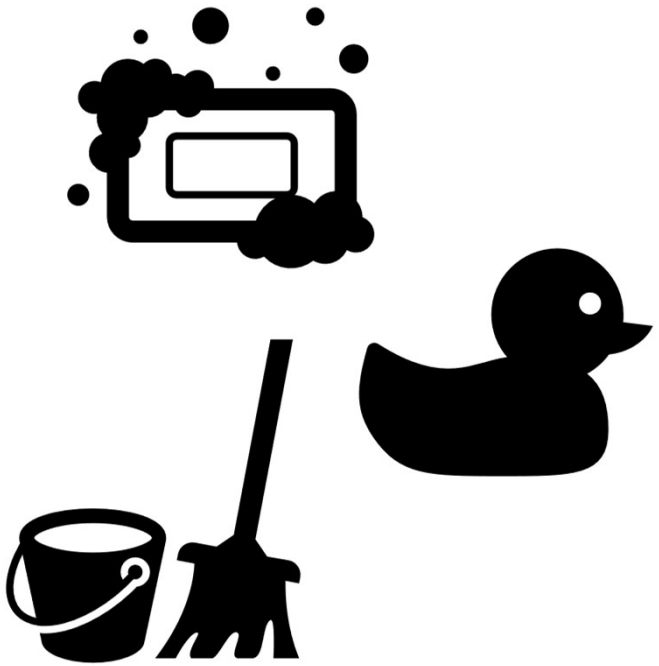
- After lifetime cycles of reprocessing the markings must still be legible
- Number of reprocessing cycles: 100

Test specification:

- 59 Products
- Products are reprocessed 100 times

Acceptance criterion:

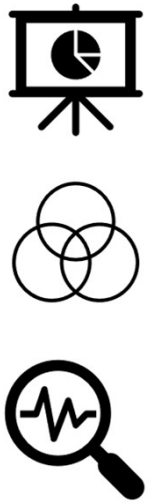
- After 100 reprocessing cycles on 59 samples, the marking must still be legible



Relevance of Statistics beyond Process Validation

Fields of application within MedTech acc. to Dr. W. Taylor

- Process Validation
- Manufacturing Acceptance Sampling Plans and Inspections
- Design Verification
- Component / Material Qualifications
- Design Validation
- Audits and Effectiveness Checks
- Test Method Validation
- Trending Data
- Setting Specifications



Statistics

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Statistics

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Risk-based approach and statistical methods in process validation

seleon GmbH > Regulatory Affairs > Risk-based approach and statistical methods in process validation

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12. October 2023

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Germany

seleon GmbH

Medtech Consulting, Product Development and Production

Our Vision

High-Class Medical Technology – First Class Service

Business areas

Engineering

Consulting

Production

Company History

1998-2008

- 1998 – Founding of the scientific consulting group in Freiburg – consulting/software development
- 2000 – Founding of heptec hardware engineering gmbh in Dessau – hardware development
- 2000 – Development of customer-specific devices, hardware and software
- 2002 – Merger to form seleon gmbh
- 2002 – Certified according to ISO 9001 & ISO 13485
- 2003 – Establishment of device production as a second pillar with a production hall in Dessau and introduction of an ERP system
- 2004 – Development of an in-house product for nasal high-flow ventilation TNI medical®
- 2007 – Separation of the in-house product business into TNI medical AG
- 2007 – Relocation of the head office to Heilbronn, as Zukunftsfonds Heilbronn (zfhn) becomes the new main shareholder

2009-2013

- 2010 – Moved into the new company building in Zukunftspark 1 in Heilbronn
- 2011 – Development of the in-house product line for cardio-logical rehabilitation Cardiowise®
- 2011 – Continuous growth in the development area + expansion of the consulting business

- 2013 – Sale of the own product division Cardiowise®
- 2013 – Focus on the service business of system development, device manufacturing and consulting

2014-2023

- 2014 – Foundation of the Consulting business unit for quality management and regulatory affairs as the third pillar
- 2015 – Extension of the consulting spectrum to include the CRO area
- 2016 – Expansion of system development projects across locations in Heilbronn, Dessau and with a strategic development partner in Romania
- 2020 – Structural adjustment
- 2020 – Focus of engineering on anaesthesia / ventilation technology, human fluid management, physiological monitoring / diagnostics, standalone software
- 2020 – Opening of an office for consulting in Hamburg
- 2021 – Opening of an office for software development in Leipzig and moved into the new company building in Zukunftspark 9 in Heilbronn

Locations


HAMBURG
DESSAU
LEIPZIG
HEILBRONN
CONSULTING
(SHARED OFFICE)
PRODUCT
DEVELOPMENT
PRODUCTION
PRODUCT DEVELOPMENT
CONSULTING
ADMINISTRATION
PRODUCT DEVELOPMENT /
SOFTWARE
seleon

Key facts

SALES
€ 13 million

EMPLOYEES
100

Product development
50 employees

Consulting
27 employees

Production
13 employees

Administration / management
10 employees

Business areas

Engineering

Consulting

Production

Business Unit Consulting

We are not “THE CONSULTANTS“, but engineers, clinical and approval experts as well as quality managers whose in-depth specialist knowledge is based on a large number of international development, manufacturing and approval projects for medical devices.

Our customers benefit from this expertise – startups, small and medium-sized companies as well as corporations – with consultative and executive support

- for all development-accompanying regulatory topics,
- for writing technical documentation,
- for clinical or performance assessments and studies,
- for European and international approval,
- for corporate processes and certifications,
- for taking on regulatory roles (manufacturer, authorised representative),
- when digitising your documentation and processes.

Travelling safely through the regulatory jungle –

So that your innovations don't burst before they reach the market.

Business Unit Consulting – Services

Consulting products

Regulatory Affairs

- Regulatory Affairs/Technical Documentation (MDR, IVDR, FDA)
- International approvals (MDSAP and other countries)
- Biological Risk Evaluation, Material Compliance

Clinical Affairs

- Clinical & Market Strategy Consulting
- Clinical Evaluation/Performance Evaluation (MDR, IVDR)
- Clinical Investigations/Performance Studies (MDR, IVDR)
- Post Market Surveillance/Clinical/Performance Follow-up

Life Cycle Processes

- Implementation of QM systems (MDR, IVDR, QSR, ISO 13485)
- Life cycle process consulting
- Risk Management & Usability engineering consulting

Software

- Software life cycle processes/Documentation
- Medical apps, DiGA & Health Software
- Artificial Intelligence & Cybersecurity in medical devices

Regulatory Business & Product Consulting

- seleon Regulatory & IP Due Diligence Services
- Technology consulting (ENG + CON + PROD)
- Assuming the role of the "Legal manufacturer"
- Assuming the role of "EU Authorized Representative"

Digitization

- Digitization of Technical Documentation
- eQMS, ALM & PLM systems, Workflow digitization
- Digital Computer System Validation (D-CSV)

We deliver regulatory News & Updates

We inform you continuously and always up-to-date about the most important topics from all areas of medical technology.

The approvals of medical technology products for first-time market introduction are subject to special approval procedures. The heterogeneous international procedures and regulatory requirements are continuously changing and becoming more and more extensive. We provide you with ongoing and always up-to-date information on the most important topics from all areas of medical technology.

www.seleon.com/en/regulatory-affairs/

Regulatory Affairs
The approval of medical devices is complex and often confusing. We clarify ...

Clinical Affairs
Medical devices require numerous verifications and assessments. What we know about this ...

Quality-management
Medical devices are subject to strict quality assurance requirements. We know the details ...

Development Excellence
Product development in medical technology is subject to its own laws. We bring light into the dark ...

CLINICAL AFFAIRS

25.10.2021

AVOIDING NEEDLESS SIDESTEPPING

Since May 2021, good preparation and a lot of stamina are important magic words when it comes to implementing the requirements of the German MPDG for clinical investigations under the MDR. To avoid any unpleasant surprises, seleon informs you.

> Straight to the investigation

Support over the entire product life cycle

customer's core tasks

seleon's network

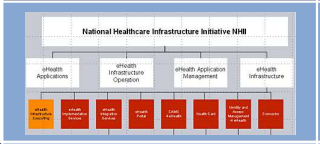
General Management	Risk Management (Business-related)	Legal Affairs & Insurances	Compliance Management	Product Portfolio Management	Infrastructure & IT
Sales	Installation, Service	User Training	Personnel management (HR services)	Finances, Accounting, Taxes, ERP System	Market analysis/ observation
Marketing	Funding	Intellectual Property (IP) Management	Innovation Management	Product Management	Reimbursement Management
Business Pro-cesses & Quality Management	Product Development	Risk Management (Product-/ process-related)	Usability Engineering	Purchasing	Stock, Logistics, Shipping
Production	Quality Assurance	Prod. Maintenance & Sustaining Engineering	Regulatory Affairs	Clinical Affairs	Complaint Handling & Vigilance

seleon's core competences

fundamental activities in case seleon is the legal manufacturer

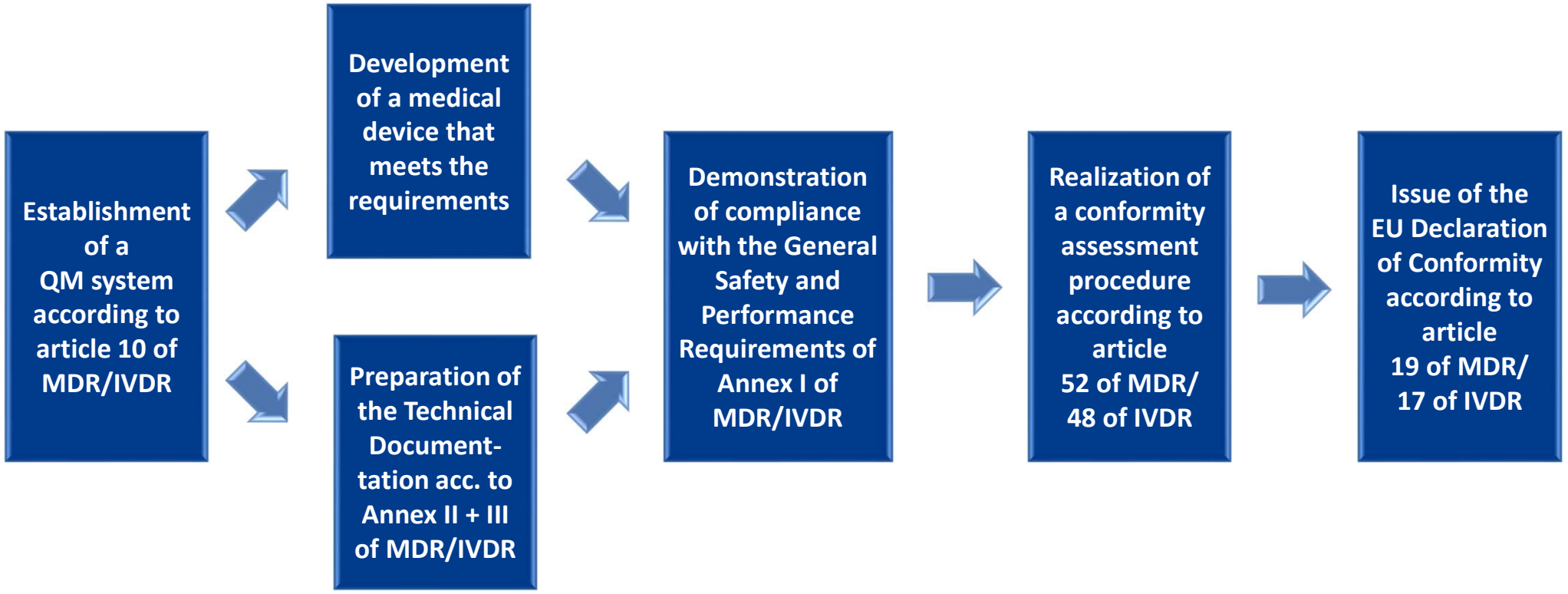
Profit from our strengths

Cases

	Establishment of QM system in newly founded Siemens Business Unit	FDA pre-submission for tanning salon products	Development of QM system and technical documentation for start-up company	PM, Requirements Engineering and Regulatory Support for Surgical Roboter	Collaboration in the MDR Remediation & Improve project of a Medtec Group	Establishment of QM systems and technical documentation for mask manufacturers
						
Project description	▪ Establishment of a QM system for a business unit with two locations, three product areas and approx. 150 employees ▪ Initial implementation of a novel software life cycle model ▪ Support of initial QM certification	▪ Preparation of an FDA 510(k) pre-submission ▪ Revision of technical documentation and preparation of FDA 510(k) submission ▪ Revision of the QM system with regard to the requirements of 21 CFR 820	▪ Establishment of a QM system ▪ Preparation of the technical documentation and support during the approval process ▪ Conduction of clinical evaluation and support clinical and usability study	▪ Assumption of project management tasks ▪ Requirements engineering support ▪ Assumption of tasks in the area of regulatory affairs ▪ Admission support	▪ Conceptual support for the transition to MDR ▪ Recording of operational and material data and preparation of biological risk assessments ▪ Ensuring material compliance ▪ Preparation of parts of the technical documentation ▪ Concept consulting for the solution of OEM-PLM constellations	▪ Realisation of a variety of consultancy projects in the context of protective equipment in the Covid 19 pandemic ▪ Establishment of QM systems according to MDR ▪ Support with admission tests ▪ Preparation of the technical documentation ▪ Conducting the Clinical Evaluation
Duration	9 months	12 weeks	2 years	3 years	3 years	since 03.2020
Scope	2 employees at 100%	3 employees at 100%	up to 5 employees	up to 3 employees	up to 5 employees	up to 10 employees

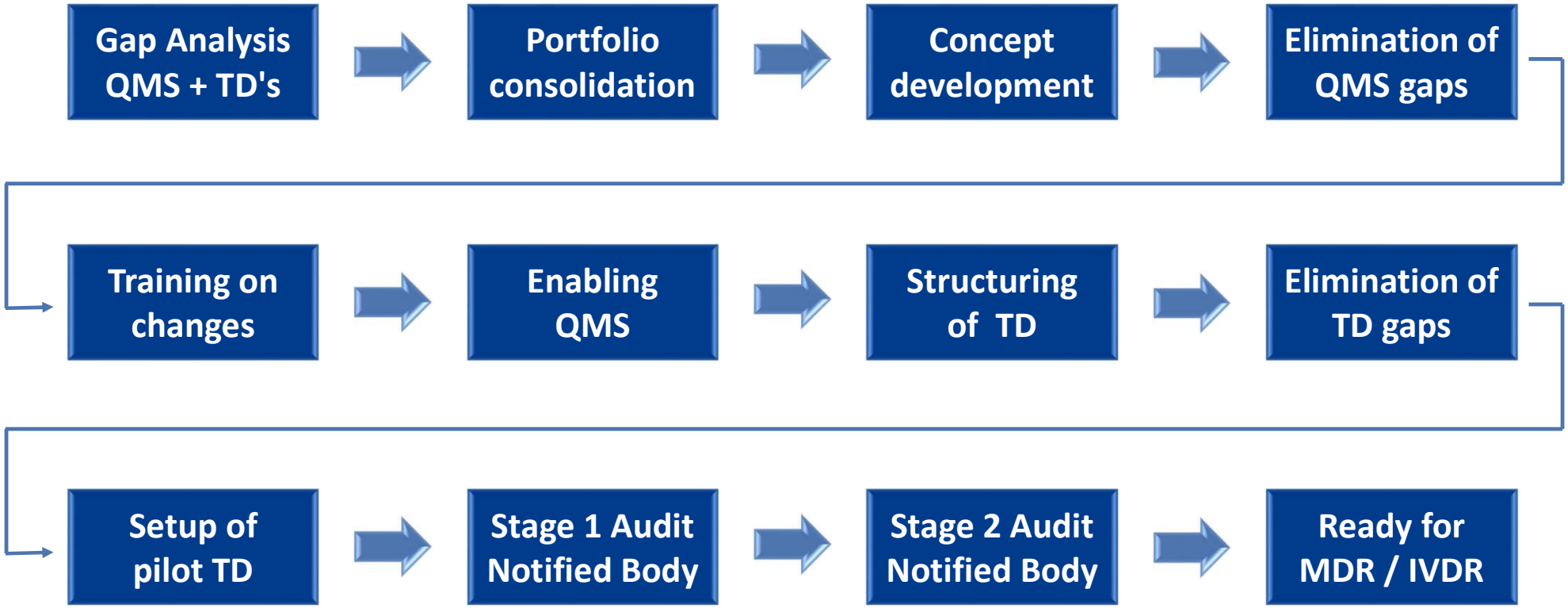
Conformity Assessment for IVD-/Medical Devices

How do I get the CE mark for my product?



Conformity Assessment for IVD-/Medical Devices

How do I get my Medical Devices fit for MDR / IVDR?



Key facts

More than 150 projects per year, from concept workshops to complete company conversion to MDR or IVDR.

More than 20 experienced colleagues support you – also on site

Every two weeks, we publish a specialist article on regulatory hot spots at www.seleon.com/en/regulatory-affairs/

Business areas

Engineering

Consulting

Production

Business Unit Engineering

In partnership with national and international customers, seleon develops individual solutions for complex medical technology devices. Through extensive engineering knowledge and years of experience, we consistently and efficiently implement your ideas in medical-technical products and lead them safely towards “time to market“.

In particular, the professionalism of our experts in the areas of system engineering, design, electronics, software and firmware allows us to fall back on a multitude of technologies. Our customers benefit from the specialist knowledge of the interdisciplinary development teams across the entire product development process – from conception to the development of functional models, prototypes and final products.

As medical technology experts, we observe all relevant regulations and applicable standards right from the start of the design phase.

From the idea to market readiness – **Our development**

Business Unit Engineering

Customised system development

Region
Central Europe

Market segments			
Medical devices (active)	**In vitro diagnostics** (IVD)	**Combination devices** (Drug device)	**Medtech software** Software / Embedded software / Apps

Areas of expertise				
	Anaesthesia and ventilation technology	**Human fluid management**	**Physiological monitoring/diagnostics**	**Software (Standalone)**
Project applications	▪ CPAP, AutoCPAP, BiLevelCPAP ▪ Home ventilation ▪ Intensive ventilation humidifier ▪ Electronic gas mixer ▪ Ventilators	▪ Contrast agent injector for CT ▪ Contrast medium injector for MRI ▪ Inhalers ▪ Medication pump ▪ Wound suction ▪ Dialysis ▪ Peritoneal dialysis	▪ Non-invasive blood pressure measurement ▪ Cardiology ▪ Blood gas analysis ▪ Oncology (tumour detection) ▪ POCT/PON lateral flow based diagnostics ▪ POCT/PON PCR based diagnostics	▪ Digital health application ▪ Network connection of existing systems ▪ Home care solutions ▪ Cloud (data/management, data analysis) ▪ Internet of Medical Things ▪ SW/app maintenance

Expert fields					
Design (UI Design)	**System integration**	**Fluidics - liquid**	**Fluidics - gas**	**Optical measurement**	**Software and Embedded**

Key facts

More than 400 projects of varying complexity, from a few person-months to 40 person-years

Certified according to DIN EN ISO 13485:2016

~ 90 patent registrations (own and for customers)

Business areas

Engineering

Consulting

Production

Business Unit Production

The production area – as one of three business areas of seleon GmbH – has been involved in the assembly and testing of predominantly electromechanical assemblies and devices in the active medical technology segment for more than 20 years.

In partnership with our supplier and service provider network, which has grown over the decades, we manufacture highly complex medical devices for you in accordance with DIN EN ISO 13485: 2016 and, on request, also offer a regularly recurring service in our service centre in Dessau.

The specialist departments Customer Care, Procurement, Production Engineering, Quality Assurance and Logistics ensure comprehensive all-round order support that does not require any further action and ensures that your device is produced and delivered to you in the desired time, cost and quality framework.

Assembly/service and testing

of mechanical and electromechanical assemblies/ systems

Business Unit Production

Assembly, testing of mechanical and electromechanical systems

Production on 1,500 m² from small series (3 – 100 items) to series (approx. 10,000 items)
▪ Design transfer in cooperation with engineering
▪ ERP master data structure (parts lists, work plans, production instructions, test instructions)
▪ Supplier management of the partner network
▪ Material procurement
▪ Warehousing and inventory financing
▪ Assembly / service of assemblies and end devices
▪ Service separate from series production
▪ Intermediate and final tests including electrical tests
▪ Quality assurance
▪ Logistics (centralised or, if desired, decentralised dispatch of goods)
▪ **Two-shift operation and Saturday work at short notice, possible in ~ 14 days**
▪ **Lean methodology: One-Piece-Flow, CIP, 5S, 7-Muda**

Equipment
▪ Design and manufacture of manufacturing/testing equipment (own workshop)
▪ Production and service environment ESD-compliant
▪ Test equipment management with a database
▪ Electrical tests according to VDE 0701-0702, IEC 60601-1, high voltage test up to 5 kV
▪ Pest control according to FDA 21 CFR part 820
▪ Indoor climate monitoring in storage, production and service areas
▪ Hazardous material cabinets
▪ Medical compressed air (10.0 bar) according to ISO 8573-1: 2010 and DIN EN 12021: 2014
▪ Dynamic warehousing with FEFO or FIFO principle
▪ ERP system: master data, serial number management, order control, procurement
▪ Product traceability
▪ Established CAPA process with direct feedback to engineering and/or the customer

Key facts

1 to 10,000 units p.a.

Scalable ERP system

Production in compliance with all applicable medical technology requirements (ISO, GMP ...)

Complete supply chain including international logistics concepts

Why seleon? We advise & implement. Targeted & hands-on.

- Many years of experience in introducing new regulations and implementing new regulatory requirements for products and processes
- Use of the know how of experienced experts in our interdisciplinary team (natural scientists, engineers, doctors, auditors, ...)
- High planning reliability in terms of times, budget and quality through a project realization as planned with our experienced project managers
- Training your employees on site so they can do it themselves
- Broad range of services:
  Adaptation of processes, QM system & Technical documentation, preparation of clinical/performance evaluations & management of clinical/performance investigations/studies, support in process optimization as well as internal, certification, MDSAP and supplier audits, approval of medical apps/DiGA & health software, assumption of regulatory roles, etc.

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