Clinical Evaluation & Clinical Performance Evaluation

Copenhagen 2018-06-11

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Agenda

- Clinical evaluation according to MDR
  - Regulatory context
  - Clinical evaluation – general
  - Clinical evaluation – what's new?
  - Where to start?
- Clinical performance evaluation according to IVDR
  - Regulatory context
  - Performance evaluation – general
  - Clinical performance evaluation – what's new?
  - Where to start?

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Clinical Evaluation According to MDR

5.5.2017 EN Official Journal of the European Union L 117/1

I

(Legislative acts)

REGULATIONS

REGULATION (EU) 2017/745 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

of 5 April 2017

on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC

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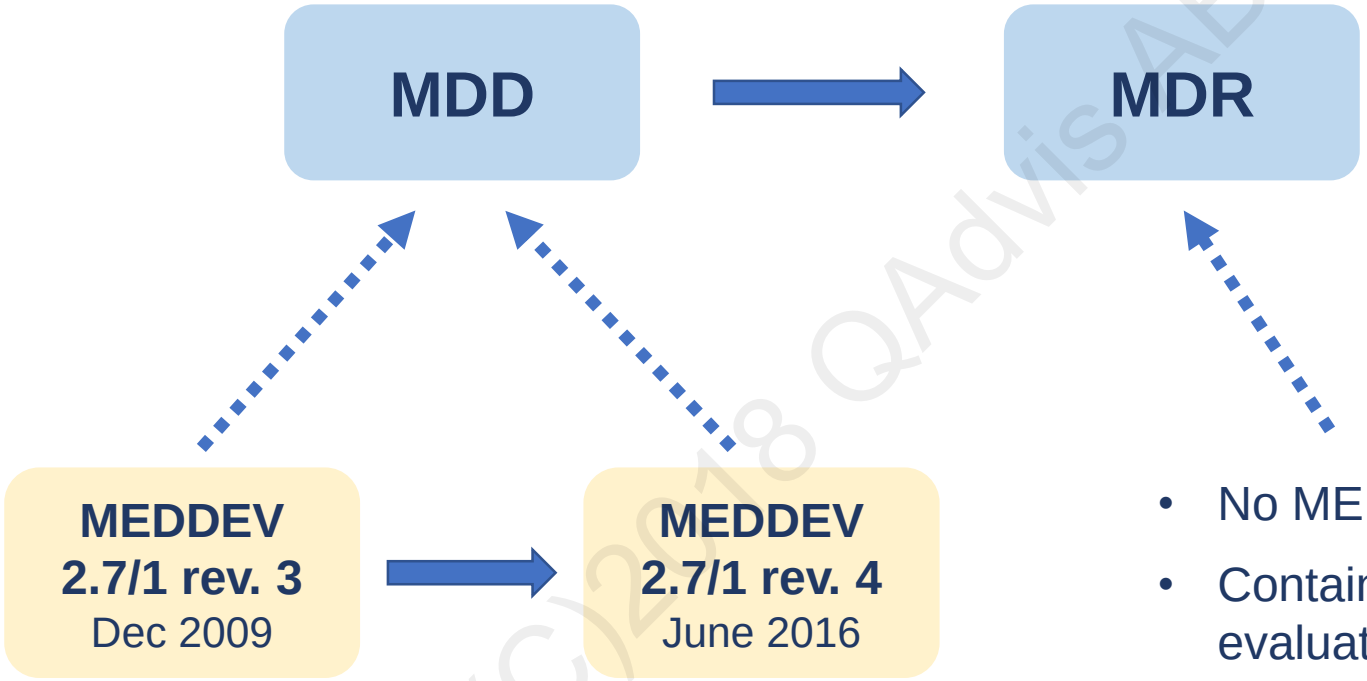
Regulatory Context



- No MEDDEV
- Contains details on clinical evaluation e.g. Article 61 and Annex XIV

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Clinical Evaluation – definition

Definition

A systematic and planned process to continuously generate, collect, analyse and assess the clinical data pertaining to a device in order to verify the ***safety and performance****, including clinical benefits, of the device when used as intended by the manufacturer*

→ Fulfillment of the General Safety and Performance Requirements?

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Clinical Evaluation – outcome

Enough data to draw conclusions	Appropriate GSPR fulfilled	
yes	yes	→ CE mark
yes	no	→ re-design / modification of intended use
no	-	→ clinical investigation

GSPR = general safety and performance requirements

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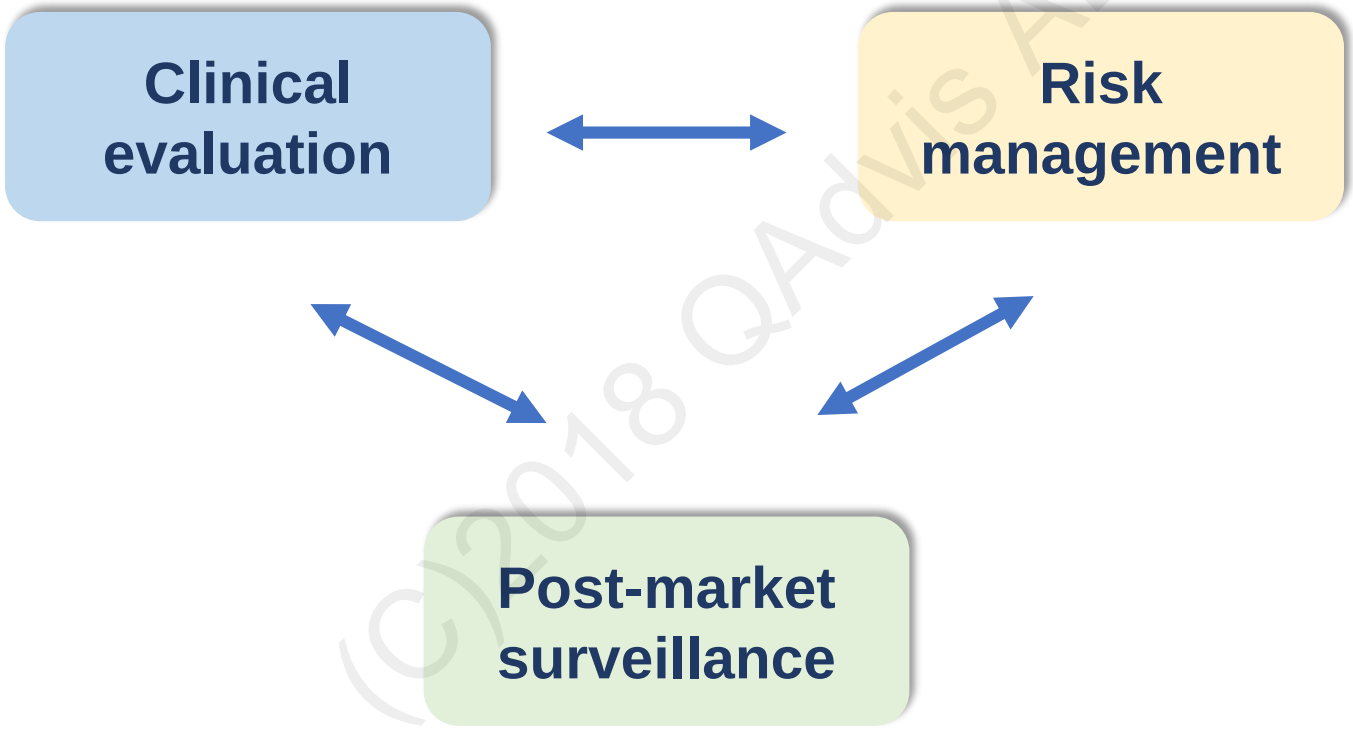
Clinical Evaluation – not an independent activity



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Clinical Evaluation – content according to MDR

1. Clinical evaluation plan
2. Literature review
3. Appraisal of clinical data
4. Analysis of clinical data

Generation of additional clinical data, if needed

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MDR vs Clinical Evaluation

- General requirements on safety and performance
- Clinical evaluation requirements
- Clinical investigation requirements
- Implantable devices and class III devices
- Expert panel
- Clinical data sources
- Equivalence
- Post-market surveillance / Post-market clinical follow-up
- Eudamed

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General Safety and Performance Requirements

Medical Device Regulation - MDR	
GSPR 1	*Devices shall **achieve the performance intended** by their manufacturer and shall be designed and manufactured in such a way that, during normal conditions of use, they are **suitable for their intended purpose**. They shall be **safe and effective** and shall **not compromise the clinical condition or the safety of patients**, or the safety and health of users or, where applicable, other persons, provided that any risks which may be associated with their use constitute **acceptable risks when weighed against the benefits** to the patient and are compatible with a high level of protection of health and safety, **taking into account the generally acknowledged state of the art.***
GSPR 8	*All known and foreseeable risks, and any undesirable side-effects, **shall be minimised and be acceptable when weighed against the evaluated benefits** to the patient and/or user arising from the achieved performance of the device during normal conditions of use.*

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Clinical Evaluation Requirements

- Strong focus on clinical evaluation
  clinical evaluation mentioned 139 times
- Detailed requirements
- Article 61 and Annex XIV
- Review of Notified Body assessments by responsible authority
  ...shall review an appropriate number of Notified Body assessments of manufacturers' technical documentation, ***in particular the clinical evaluation documentation****...*

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Clinical Evaluation Requirements - Examples

- Clear specification of target groups with clear indications and contraindications
- Detailed description of clinical benefits to patients with relevant and specified clinical outcome parameters
- Specification of methods for examination of qualitative and quantitative aspects of clinical safety – determination of residual risks and side-effects
- Specification of parameters used to determine the acceptability of the benefit-risk ratio – based on state of the art

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Clinical Investigation Requirements

- Strong focus on clinical investigation
- Article 62 and Annex XV
- Refers to ISO 14155:2011
  Clinical investigation of medical devices for human subjects – Good clinical practice
- Includes much of the ISO 14155:2011 information
- Detailed list of conditions that have to be met to conduct a clinical investigation
  including device requirements (fulfillment of GSPR)
- Detailed information
  e.g. studies on children, studies in emergency situations etc.

GSPR = general safety and performance requirements

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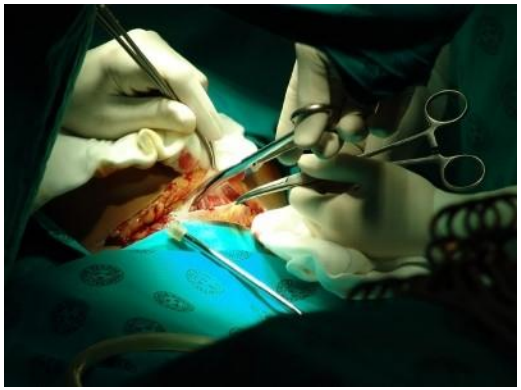
Implantable Devices and Class III Devices



- A clinical investigation is generally required
- Exceptions as listed in Article 61 (4 - 6)
  - **Modifications of already existing, equivalent device**, marketed by the same manufacturer, which has appropriate clinical data and clinical evaluation.
  - **Device equivalent to existing device, marketed by other manufacturer**, where the clinical evaluation has been performed according to MDR. **Requires continuous access to technical documentation and a contract between the manufacturers.**
  - **Device placed on the market according to MDD or AIMDD which has sufficient clinical data** and is in compliance with any product-specific common specification.

Common specification = technical and/or clinical requirements, other than a standard, that provides a means of complying with legal obligations

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Expert Panel

- Implantable devices and some class IIb devices (devices intended to administer and/or remove a medicinal substance)
- Voluntary consultation of expert panel, designated by the European Commission, regarding clinical strategy
- Additional scrutiny process: Notified Body's clinical assessment report to be scrutinised by expert panel

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Clinical Data - sources

- Information on safety or performance that is generated from the use of a device
- Sources:
  a) Clinical investigation(s) of the device
  b) Clinical investigation(s) or other studies reported in scientific literature of equivalent device
  c) Reports published in peer reviewed scientific literature on other clinical experience of either the device or equivalent device
  d) Post-market data

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Clinical Data – Is it needed?

- *Confirmation of conformity with relevant general safety and performance requirements...shall be based on clinical data*

  Article 61 (1)

- *... adequate justification for any such exception ... based on ...*
  - risk management
  - the interaction between the device and the human body
  - the clinical performance intended
  - the claims of the manufacturer

  Article 61 (10)

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Equivalence

- Technical – biological – clinical characteristics have to be comparable (same / similar)
- All components (technical – biological – clinical) from the same device
- Manufacturer needs to have *sufficient levels of access to the data relating to devices with which they are claiming equivalence*

Implantable and class III devices: Requires continuous access to technical documentation and a contract between the manufacturers

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Post-Market Clinical Follow-Up (PMCF)

- A continuous process that updates the clinical evaluation
- Part of post-market surveillance
- Proactive collection of data
- Confirm safety and performance of the device
  - side-effects; already known / new
  - acceptability of benefit/risk ratio
  - verification of intended use (identification of misuse / off label use)
- Output: PMCF evaluation report

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Eudamed - European Database on Medical Devices

- Registration of devices
- UDI database
- Economic operators registry
- Notified Bodies and certificates registry
- **Clinical investigations**
- Vigilance and post-market surveillance
- Market surveillance

UDI = Unique Device Identification

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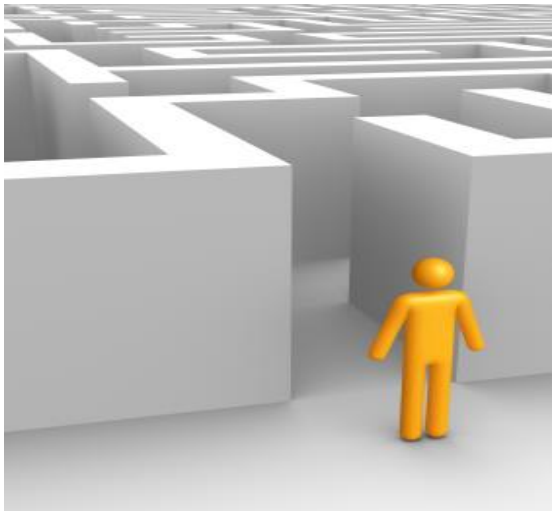
Where to Start?



First step

Update clinical evaluation reports to be in compliance with revision 4 of MEDDEV 2.7/1

– *not sufficient to fulfill MDR but a good start*

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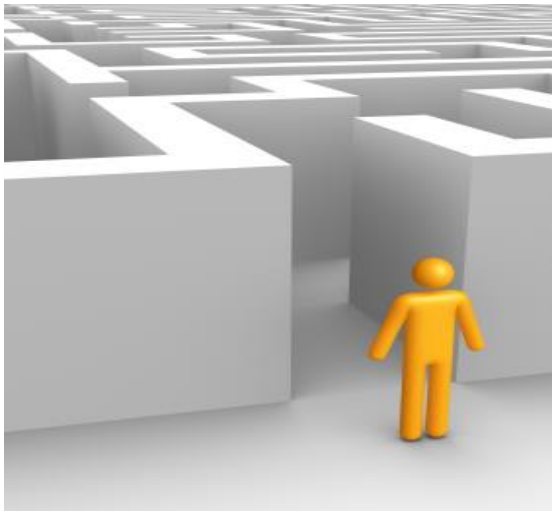
Where to Start?



Second step

- In-depth review of clinical data for every single device
- Extra attention
  - if equivalence is claimed
  - for class III and implantable devices
- Conclusions:
  - Sufficent clinical data available?
  - Sufficent level of access to technical data for equivalent device(s)?
  - Need for clinical investigation?

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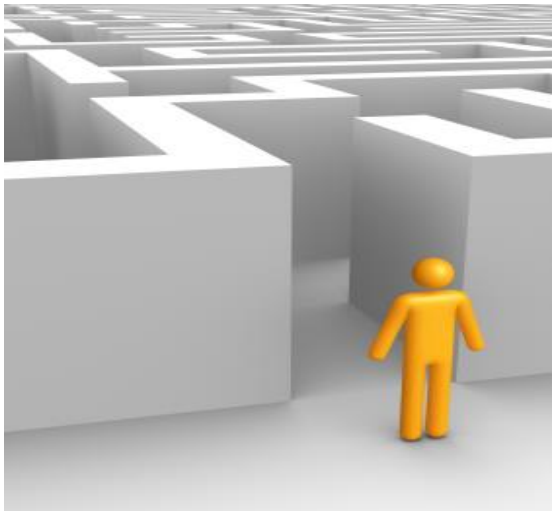
Where to Start?



Quality Management System

Update Quality Management System with regard to clinical evaluation, clinical studies and post-market surveillance / post-market clinical follow-up

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Clinical Performance Evaluation According to IVDR

REGULATION (EU) 2017/746 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

of 5 April 2017

on *in vitro* diagnostic medical devices and repealing Directive 98/79/EC and Commission Decision 2010/227/EU

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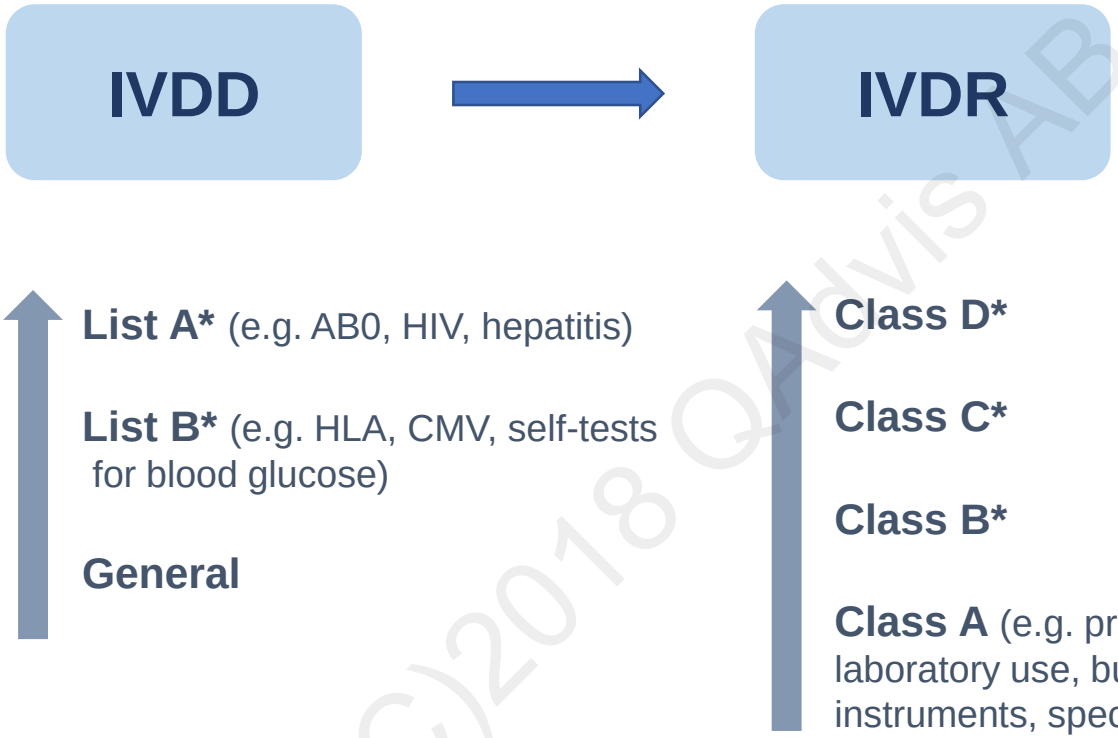
Regulatory Context



* Requires involvement of a Notified Body for conformity assessment

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Clinical Performance Evaluation – a new concept?

Term	IVDD	IVDR
Clinical performance	0 hits	90 hits
Clinical evidence	0 hits	40 hits

- No!
- Requirements on clinical performance parameters are included in IVDD
- Described in detail in GHTF documents, e.g. GHTF/SG5/N7:2012

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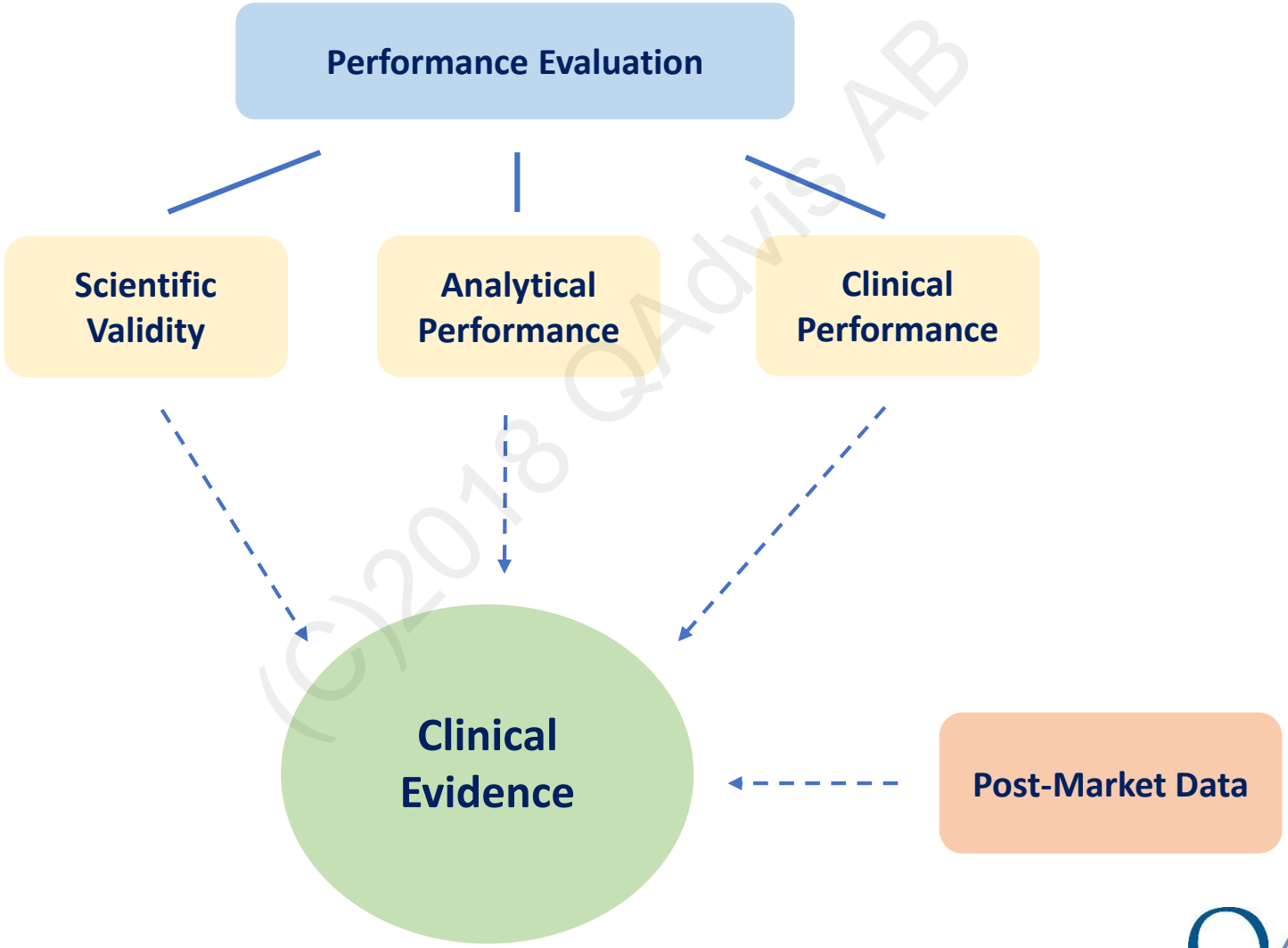
Concept Overview



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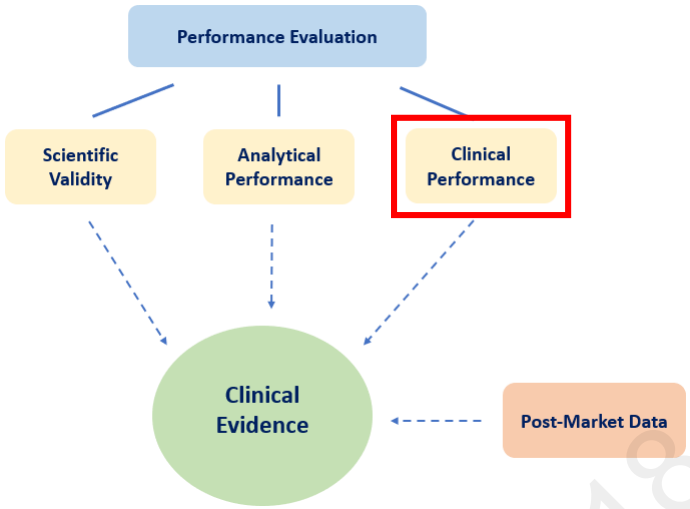
Clinical Performance - definition



- *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*

- E.g. diagnostic sensitivity, diagnostic specificity, positive / negative predictive value, expected values in normal and affected populations

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IVDR vs Clinical Performance Evaluation

- General requirements on safety and performance
- Clinical performance evaluation requirements
- Clinical evidence requirements
- Class C and D devices
- Eudamed

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General Safety and Performance Requirements (1)

In Vitro Medical Device Regulation - IVDR	
GSPR 1	*Devices shall **achieve the performance intended** by their manufacturer and shall be designed and manufactured in such a way that, during normal conditions of use, they are **suitable for their intended purpose**. They shall be **safe and effective** and shall **not compromise the clinical condition or the safety of patients**, or the safety and health of users or, where applicable, other persons, provided that any risks which may be associated with their use constitute **acceptable risks when weighed against the benefits** to the patient and are compatible with a high level of protection of health and safety, **taking into account the generally acknowledged state of the art.***
GSPR 8	*All known and foreseeable risks, and any undesirable side-effects, **shall be minimised and be acceptable when weighed against the evaluated benefits** to the patient and/or user arising from the achieved performance of the device during normal conditions of use.*

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General Safety and Performance Requirements (2)

	In Vitro Medical Device Regulation - IVDR
GSPR 9.1	*Devices shall be designed and manufactured in such a way that they are suitable for the purposes referred to in point (2) of Article 2, as specified by the manufacturer, and suitable with regard to the performance they are intended to achieve, **taking account of the generally acknowledged state of the art**. They shall achieve the performances, as stated by the manufacturer and in particular, where applicable:* *(a) the **analytical performance**, such as, analytical sensitivity, analytical specificity, 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 and handling and control of known relevant endogenous and exogenous interference, crossreactions; and* *(b) (b) the **clinical performance**, such as diagnostic sensitivity, diagnostic specificity, positive predictive value, negative predictive value, likelihood ratio, expected values in normal and affected populations.*
GSPR 9.4	*The characteristics and performances of the device shall be **specifically checked** in the event that they may be affected when the device is used for the intended use under normal conditions:* *(a) for **devices for self-testing**, performances obtained by **laypersons**;* *(b) for devices for **near-patient testing**, performances obtained in **relevant environments** (for example, patient home, emergency units, ambulances).*

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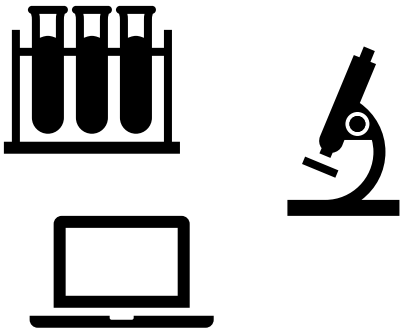
Clinical Performance Evaluation



- Detailed requirements
- Articles 57-77, Annex XIII, Annex XIV

Clinical Performance Evaluation – type of study

Interventional study	Test results may influence management decisions and/or be used to guide treatment
Study involving risks for the subjects	- Invasive procedures or other risks - Surgically invasive sample-taking
Study using left-over specimens	Specimens obtained for other purpose (routinely obtained samples)

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Clinical Performance Evaluation – type of study

	General requirements	Additional requirements	Ethical review	Authorisation by Member State(s)
Interventional study	yes	yes	yes	yes
Study involving risks for the subjects	yes	yes	yes	yes
Study using left-over specimens	yes	no	according to national law	no*

*For companion diagnostics, left-over studies shall be notified to the Competent Authority

Clinical Performance Evaluation – general requirements

- Device requirements
  (fulfillment of GSPR, except those covered by the performance study)
- Normal conditions of use
  Study to be performed in circumstances similar to the normal conditions of use, where appropriate
- Protection of study subjects
  Rights, safety, dignity, well-being
- In accordance with applicable law on data protection
- Generation of scientifically valid, reliable and robust data

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Clinical Performance Evaluation – additional requirements

- Similar requirements as for clinical studies performed according to MDR
- Refers to ISO 14155:2011
  Clinical investigation of medical devices for human subjects – Good clinical practice
- Includes much of the ISO 14155:2011 information
- Detailed list of conditions that have to be met to conduct a clinical investigation
- Detailed information
  e.g. studies on children, studies in emergency situations etc.

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Clinical Performance Study Plan (CPSP)

- Needed for all clinical performance evaluations
  (including studies using left-over specimens)
- Detailed description in Annex XIII

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Clinical Performance Study – Is it needed?

Clinical performance studies ...shall be carried out unless it is duly justified to rely on other sources of clinical performance data

Article 56 (4)

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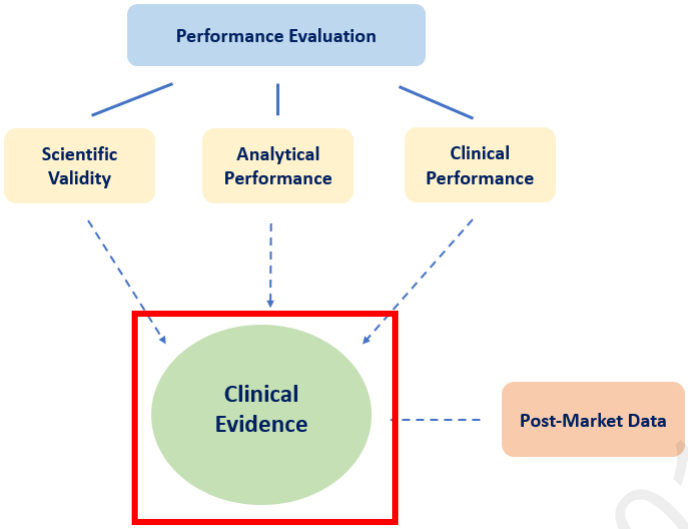
Clinical Evidence



- Documented in *Performance Evaluation Report*
- Scientific demonstration that the intended clinical benefit and safety are achieved according to the state of the art in medicine – fulfillment of GSPR
- Updated according to post-market performance follow-up (PMPF) plan (at least anually for class C and D devices)

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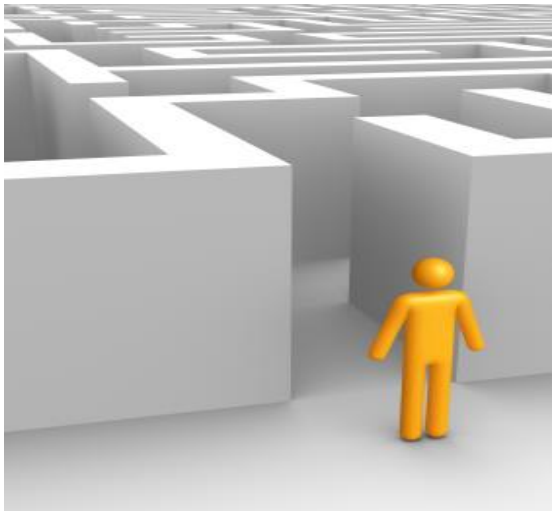
Where to Start?



First step

Device classification – Notified Body needed?

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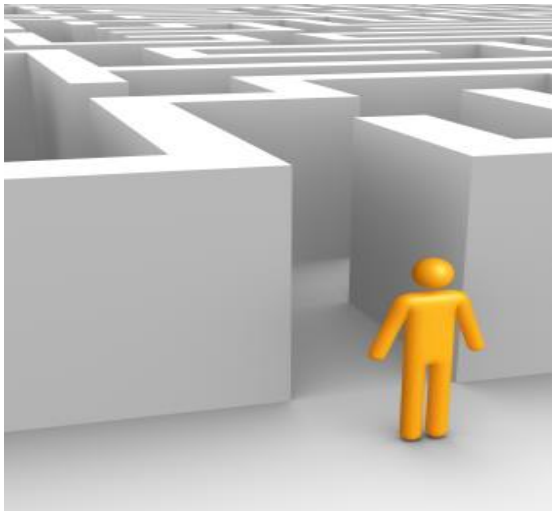
Where to Start?



Second step

- In-depth review of clinical evidence for every single device
- Draft of *Performance Evaluation Report*

- Conclusions:
  - Scientific validity supported?
  - Analytical performance supported?
  - Clinical performance supported?
  - Need for performance studies (analytical and/or clinical)?

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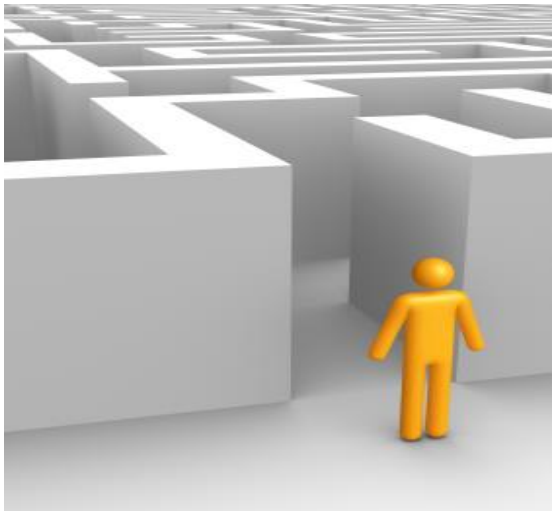
Where to Start?

Quality Management System



Update Quality Management System with regard to performance evaluation and post-market surveillance

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MDR & IVDR

- Start now
- Identify key activities
- Identify the most resource-consuming activities
- Keep you informed

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