MDR/IVDR: continuous improvement paradigm

Hugo, Rick, Robyn, Gert
Things we partially know …
But some have a nasty sting ...

Trend analysis

QMS & pdca

Common specifications

Continous improvement

Clinical evaluation

EU DAMED

LiABiLiTy

Plan

Act

Do

Check

PDCA Methodology

- Deploy
- Confirm with plan

- Measure & Monitor
- Confrimmity & effectiveness

- Analyze and Review
- Decide and Change
- Improve effectiveness
Process

Plan (P)

Report (R) / Summary (S)

Clinical Investigation
- CIP

Literature search
- LSP

Clinical Evaluation
- CER

Safety and clinical performance (implantable and class III)

Safety and clinical performance (SSCP)

Post-Market Clinical Follow-up
- PMCFP

Post-Market Surveillance
- PMSP

Vigilance

Incidents/Trends

Periodic Safety Update

PMCFR

PMSR

PSUR

*the practical approach*
EU MDR: CLINICAL EVALUATION

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DIRECTOR, MEDICAL AND CLINICAL AFFAIRS, ABBOTT LABORATORIES
The views and opinions expressed in this presentation are those of the presenter and do not necessarily reflect the official policy or position of any agency or company.

Presentation materials may come from various resources including EU MDR regulation, NB presentation, conferences and competency authority guidance.
CLINICAL IS ONE OF THE BIGGEST CHANGES IN EU MDR

Notified Bodies
- Level playing field
- Better oversight
- Joint inspection of NBs
- Unannounced audits

Clinical Evidence
- Harder equivalency pathway
- Proactive post-market clinical follow-up
- Integration of clinical, RM and PM

Vigilance
- Increased coordination among Member States
- Strengthened Post-market surveillance
- Public safety, trend and performance data

Transparency
- Eudamed database
- Scrutiny of high risk Devices
- Traceability/UDI

~50% MDR regulation is related to clinical
EQUIVALENCY REQUIREMENT

Technical
- be of similar design
- used under similar conditions of use
- have similar specifications and properties (e.g. physicochemical properties such as intensity of energy, tensile strength, viscosity, surface characteristics, wavelength, software algorithms, porosity, particle size, nanotechnology, specific mass, atomic inclusions – nitrocarburising, oxidability)
- use similar deployment methods (if relevant)
- have similar principles of operation and critical performance requirements

Biological
- use same materials or substances in contact with the same human tissues or body fluids
- for a similar kind and duration of contact and similar release characteristics of substances
- including degradation products and leachables
- Exceptions can be foreseen for devices in contact with intact skin and minor components; in these cases risk analysis results may allow the use of similar materials taking into account the role and nature of the similar material. Evaluators should consider biological safety (e.g. ISO 10993) as well as other aspects necessary for a comprehensive demonstration of equivalence. A justification explaining the situation should be provided for any difference.

Clinical
- used for the same clinical condition or purpose (including similar severity and stage of disease)
- at the same site in the body
- in a similar population (including age, gender, anatomy, physiology)
- have same kind of user
- not foreseen to deliver significantly different performances
- have similar relevant critical performance according to the expected clinical effect for a specific intended purpose
CLINICAL EVALUATION AND INVESTIGATION IN EU MDR

Clinical Evaluation Article 61
- Annex I, IO: Chemical safety
- Annex I, IO, 12, 13: Biological safety
- Annex I, 16, 17: Radiation and electronic programmable
- Annex I, 18, 19: Active Device and Implantable
- Annex II, 6, 7: Pre-clinical and clinical data
- Annex XIV, 1.3: Technical, Biological, Clinical

Commercial and Reimbursements

Regulatory Requirement

Clinical Evaluation Plan
- Annex XIV, 1. Clinical Evaluation
- Annex I, 1, and 8: Benefit-risk determination

Clinical Strategy (Clinical Evidence Acquisition plan)
- Article 2 (48): Clinical Data Definition:
  - Annex II, 6.1: Pre-clinical and clinical data
- Annex XIV, 1: Clinical Evaluation
- Scientific Literature
- Exploratory investigations,
- Feasibility and pilot studies
- Pilot clinical investigations
- Post-market clinical follow-up

Post Market Clinical Follow-up Plan and Report
- Article 61 (11)
- Annex XIV, Part B

Clinical Investigation Process (Registry, Pilot, etc)
- Article 62 and 72: General Requirement
- Article 62-69: Consideration for patient safety
- Article 70: Application
- Article 73: Electronic system
- Article 75 and 77: Updates and reports
- Annex II, 6.1: Pre-clinical and clinical data
- Annex XIV, Clinical Investigation

Risk Analysis Report (for input to CEP)

Preliminary Design FMEA (for input to CEP)

Clinical Evaluation Report
- Article 61 (12)
- Annex XIV, Part A-4

Clinical Evaluation Report
- Article 62, 72
- Annex XV, Chapter III-7
INTERLINKAGES AMONG CLINICAL EVALUATION, RISK AND POST MARKET

- Risk Plan
- Risk Files
- Risk Summary

- Clinical Evaluation Plan
- Development Plan
- Literature Review Plan and Summary
- Clinical Evaluation Report
- Post Market Clinical Follow-up (PMCF) plan and report
- Summary of Safety and Clinical Performance

- Post-market surveillance (PMS) Plan
- PMS Report
- Periodic Safety Update Report (PSUR)
# Clinical Evaluation is the Cornerstone

<table>
<thead>
<tr>
<th>Report</th>
<th>Class I</th>
<th>Class IIa</th>
<th>Class IIb</th>
<th>Class III &amp; Implants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Evaluation plan (CEP) and Report (CER)</td>
<td>When needed</td>
<td>2-5 years</td>
<td>2-5 years</td>
<td>Annually</td>
</tr>
<tr>
<td>Post-Market Clinical Follow-Up (PMCF) Evaluation Report</td>
<td>When needed</td>
<td>When needed, or at least every 2-5 years</td>
<td>When needed, or at least every 2-5 years</td>
<td>At least annually</td>
</tr>
<tr>
<td>Summary of Safety and Clinical Performance (SSCP)</td>
<td>N/A</td>
<td>Every 2 years</td>
<td>Every 2 years</td>
<td>Annually</td>
</tr>
<tr>
<td>Consultation, Scrutiny</td>
<td>N/A</td>
<td>N/A</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Risk Management Report</td>
<td>N/A</td>
<td>N/A</td>
<td>Regular systematic update</td>
<td></td>
</tr>
<tr>
<td>Product Safety &amp; Usability Report (PSUR)</td>
<td>N/A</td>
<td>At least every 2 years</td>
<td>At least annually</td>
<td>At least annually</td>
</tr>
<tr>
<td>Post-Market Surveillance Report (PMSR)</td>
<td>When needed</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>
SUFFICIENT EVIDENCE DETERMINATION IS CRITICAL
**CLINICAL INVESTIGATION IS EXPECTED FOR CLASS III AND IIB**

<table>
<thead>
<tr>
<th>Procedure</th>
<th>MDR related changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIP</td>
<td>Mainly vulnerable population section and ICF section, definition of timing for Final report, study funding language, SAE definition extension to “chronic disease” (already current version).</td>
</tr>
<tr>
<td>CSR</td>
<td>Timing for Final report is set to 12 months after LPLV</td>
</tr>
<tr>
<td>ICF</td>
<td>“Legally acceptable representative” term was taken from ICH GCP</td>
</tr>
<tr>
<td>Clinical study submissions</td>
<td>New process for submissions through EUDAMED, checklist of submitted documentation</td>
</tr>
<tr>
<td>Clinical trial registration</td>
<td>EUDAMED new platform for Clinical trial registration</td>
</tr>
<tr>
<td>Investigator Brochure</td>
<td>One additional line in MDR is required: define deviations from normal practice</td>
</tr>
<tr>
<td>Study Audits</td>
<td>Pre-CE mark and PMCF studies to receive internal targeted GCP audits</td>
</tr>
<tr>
<td>CONTENT (MDR/IVDR)</td>
<td>MDR Requirement</td>
</tr>
<tr>
<td>-------------------</td>
<td>----------------</td>
</tr>
<tr>
<td>Annex VII, IX, X</td>
<td>Reduced equivalence</td>
</tr>
<tr>
<td>Annex XVI/Annex XIV</td>
<td>Detailed rules for subject protection</td>
</tr>
<tr>
<td>Annex XIV, IX/Annex XIII, VII</td>
<td>Detailed rules for subject Proactive plans for PMCF/PMPF</td>
</tr>
<tr>
<td>Article 33,113/Article 30,113</td>
<td>EUDAMED submission</td>
</tr>
<tr>
<td>Article 4/Article 3</td>
<td>Expert panel, pre-market consultation</td>
</tr>
<tr>
<td>Annex I,II</td>
<td>Continuous assessment of risk and safety</td>
</tr>
<tr>
<td>Annex I, XIV/Annex I, XIII</td>
<td>Consider State of Art</td>
</tr>
</tbody>
</table>
CASE STUDY: PRODUCT DESCRIPTION

- Indication: FAK-B Drug Eluting Coronary Stent System is class III medical device indicated for improving coronary luminal diameters in patients with symptomatic ischemic heart disease due to de novo lesions of length ≤ 36 mm in native coronary arteries with reference vessel diameters of 2.0 mm to 4.9 mm. In addition FAK-A is indicated for treating chronic total occlusions (CTO).

- Approval: FAK-B is approved in 2013 in Europe based on equivalency of FAK-A. FAK-A is the previous generation stent with same drug coating with clinical study-A.

- Comparing with FAK-A, FAK-B:
  - Same metal and same drug
  - Same manufacturer
  - Use E-Wire technique to wrap around a denser metal for better usability
    - Increase radiopacity
    - Thinner struts
## CASE STUDY: DATA

<table>
<thead>
<tr>
<th>Clinical Data ¹</th>
<th>FAK-A</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Study Design</td>
<td>Non-randomized, open label, interventional study</td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>500</td>
<td></td>
</tr>
<tr>
<td>Target Lesion Failure</td>
<td>Year 1: 6%</td>
<td>Year 2: 8%</td>
</tr>
<tr>
<td>Device success</td>
<td>98%</td>
<td></td>
</tr>
<tr>
<td>All death rate</td>
<td>Year 3: 5%</td>
<td></td>
</tr>
</tbody>
</table>

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### Exceptional Usability ²

- **FAK-A**
- **FLK-B**

### Excellent Safety ³

- **FAK-A**
- **FAK-B**

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1. T. Johnson et al, Cardio, 2012(3):123
2. Data on file
3. Data from product registry database
Can FAK-B claim equivalency to FAK-A?

Is the data sufficient for FAK-B per MDR?
  - How to reach the conclusion of “sufficient”?

What kind of data package would you submit for clinical evaluation of FAK-B?
  - New clinical studies?
  - Existing data/reports beside study A?

What are the new/different reports expected under MDR?
EU MDR: POST MARKET SURVEILLANCE

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DIRECTOR, QUALITY SYSTEMS & BUSINESS SUPPORT, ABBOTT LABORATORIES
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### EU Medical Device Directives
- Required to complete post-market surveillance
- Post-Market Clinical Follow-up for limited types of devices
- Vigilance reporting

### EU Medical Device Regulations
- Post Market Surveillance System must be established as part of the Quality System
- Post Market Surveillance Plan required for all devices
- Risk Management and Clinical Evaluation processes are interdependent and regularly updated
- Post Market Surveillance Reports, depending on Device Class
- Expected assessment of vigilance and trend data to similar devices
- Use of the EUDAMED Database for reporting
- Increased coordination across Member States
- Increased vigilance and trend reporting with shortened reporting timeframes

Post-Market Surveillance is one of the most critical changes within the MDR.
## Magnitude of Change for PMS

<table>
<thead>
<tr>
<th>People</th>
<th>Process</th>
<th>Technology</th>
</tr>
</thead>
</table>
| Additional resources will be needed:  
  - New reports submitted  
  - Increased follow-up reporting  
  - Reporting window has decreased from 30 days to 15 days  
  - New training programs  
  - Coordination of PMS systems across businesses / divisions | New corporate level PMS and vigilance policy and process documents created  
  - Cascading effect for new and revised documents for each business / division  
  - New electronic submissions via EUDAMED | New electronic system for report submission – EUDAMED  
  - New internal tools to pull data and generate reports  
  - IT system must be assessed and implemented  
  - EUDAMED functionality may not be fully available upon MDR implementation |
POST MARKET SURVEILLANCE LIFECYCLE

Develop Medical Device
Implement risk management tools (dFMEA, pFMEA)

Complete Risk & Benefit Analysis
Confirm risks are controlled

Initial Clinical Evaluation
Confirm Claims & Assessment of Risk

Post Market Surveillance
PMCF, PMSR, PSUR, SSCP

Identify & Control Risks
Complete Hazard Analysis (dFMEA, pFMEA) and control risks

Update Clinical Evaluation & Risk Management
Inputs from PMS reports

Determine Actions Required
Product updates to maintain State of the Art

Place Updated Device on the Market
Include updated labeling and IFU’s as required

Manage throughout the lifetime of the device
PRODUCT DEVELOPMENT PROCESS

Identify Intended Benefit to Patient or User
Collect evidence of intended benefit and acceptability

Identify Risks
Identify potential risks based on intended use and clinical and post market data

Evaluate and Assess Risk
Collect evidence supporting actual risk of the device, including customer data

Eliminate Risk
Eliminate, control or reduce risks as far as possible

Risk / Benefit Analysis
Assess risk against intended benefits to ensure suitability for the market

New or updated devices should incorporate post-market data from the same or like devices into the product development process in order to reduce risk, improve usability, and enhance performance of these device.
# Risk Management/Clinical Evaluation/Post Market Surveillance

## Three Key Processes Dependent on Each Other

<table>
<thead>
<tr>
<th>Phase</th>
<th>Key Activity</th>
<th>Inputs</th>
</tr>
</thead>
</table>
| Pre-Market  | Determining Acceptability of Risk  | • Risk Tolerance  
• Type of Technology  
• Clinical Use experience |
| Product     | Justifying Acceptability of Risk   | • Product Standards  
• Literature  
• Generally Acknowledged ‘State of the Art’  
• Comparison to like products |
| Post-Market | Oversight                          | • Continuous assessment of risk  
• Risk Management Standards  
• Post-Market Clinicals  
• Post-Market Reporting |
POST MARKET SURVEILLANCE PROCESS OVERVIEW

**Plans**
- PMS Plan
- PMCF Plan

**Collect & Analyze**
- **Proactive Data**
  - Post-Market Clinical Follow-up
  - Post Launch Clinical Trials
  - Registry Studies by Manufacturer
- **Reactive Data**
  - Customer Surveys
  - User / Focus Groups
  - Patient Record Review
  - Complaint Data & Trending
  - User & Social Media Feedback
  - Literature Reviews
  - Servicing Data & Trending
  - Similar Device Information
  - Field Actions / Recalls
  - NCMR
  - CAPA & Complaint Investigations

**Reports**
- PMCF Report
- PMS Report
- PSUR
- SSCP

Throughout the lifetime of the device
Post Market inputs should drive updates within the product development process.

Risk is the combination of probability of harm and the severity of that harm.

Risk needs to be continually assessed against the intended benefit of the device.

The Risk Management/Clinical Evaluation/Post Market Surveillance process should continue to occur throughout the lifetime of the device.
MONITORING FOR THE LIFETIME OF THE DEVICE

- The Post-Market Clinical Follow-up & Post Market Surveillance Plans need to define the extent of monitoring throughout the device lifetime based on the risk and longevity of the device.
- As more data is established for the device and like devices, respective plans can be updated, as warranted.
- The process remains active until the device is no longer on the market.
PMS & TREND REPORTING

<table>
<thead>
<tr>
<th>Device Class</th>
<th>Report Type</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I</td>
<td>PMS Report</td>
<td>As needed</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Note: the Competent Authority can request at any time</td>
</tr>
<tr>
<td>Class IIa</td>
<td>PSUR</td>
<td>Minimally every 2 years</td>
</tr>
<tr>
<td>Class IIb</td>
<td>PSUR</td>
<td>Minimally every year</td>
</tr>
<tr>
<td>Class III</td>
<td>PSUR</td>
<td>Minimally every year and using EUDAMED</td>
</tr>
<tr>
<td>All</td>
<td>Trend Report</td>
<td>As trends on non-serious incidents &amp; expected side effects that impact risk benefit ratio arise</td>
</tr>
</tbody>
</table>

Field Safety Notices
Field Corrective Actions
Serious Incidents
PSUR for Class III or Implantable
EUDAMED
Trend Reports

PMS/PSUR & Trend Reports shall identify Corrective or Preventive Actions and be implemented within the PMS & Trending Processes
Indication: FAK-B Drug Eluting Coronary Stent System is class III medical device indicated for improving coronary luminal diameters in patients with symptomatic ischemic heart disease due to de novo lesions of length $\leq 36$ mm in native coronary arteries with reference vessel diameters of 2.0 mm to 4.9 mm. In addition FAK-A is indicated for treating chronic total occlusions (CTO).

Approval: FAK-B is approved in 2013 in Europe based on equivalency of FAK-A. FAK-A is the previous generation stent with same drug coating with clinical study-A.

Comparing with FAK-A, FAK-B:
- Same metal and same drug
- Same manufacturer
- Use E-Wire technique to wrap around a denser metal for better usability
  - Increase radiopacity
  - Thinner struts
CLINICAL/PMS CASE STUDY: QUESTIONS TO ANSWER

- Identify 3 Post Market Surveillance data examples that could be inputs into the drug eluting stent Product Development Process?
  - How do these 3 examples help identify and reduce the risk of a new or updated product?
- If PMS reports identify a new risk related to the product, what are 3 next step that should occur as part of the Product Development Process?
  - Explain the importance of each step you have selected.
- Is this device subject to a Post Market Surveillance Plan?
  - Explain.
- Is the PMS report requirement a Post Market Surveillance Report (PMSR) or Periodic Summary Update Report (PSUR)?
  - Why?
- For this type of device, is the required PMS Report submitted via EUDAMED or not?
  - Why?
State of the Art and the EU IVDR

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The views and opinions expressed in this presentation are those of the presenter and do not necessarily reflect the official policy or position of NSF.
State of the Art

General Safety and Performance Requirement 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.
Quiz 1

How many times is *State of the Art* is mentioned in the IVDR?
Quiz 1

> How many times is *State of the Art* is mentioned in the IVDR?
  - Answer = 20 (5x IVDD, 12x MDR)

> How is the *State of the Art* defined in the Regulation?
Quiz 1

> How many times is State of the Art is mentioned in the IVDR?
  • Answer = 20 (5x IVDD, 12x MDR)

> How is the State of the Art defined in the Regulation?
  • Answer = Not at all. Not in the IVDR, IVDD, MDR, Blue Guide......and only sometimes in Member State law.
EN ISO 14971:2012
Medical devices. Application of risk management to medical devices

• Introduction: The manufacturer makes judgments relating to safety of a medical device, including the acceptability of risks, taking into account the *generally accepted state of the art*, in order to determine the suitability of a medical device to be placed on the market for its intended use.

MEDDEV 2.7.1 rev 4 (clin eval)

> “changes concerning current knowledge/ the *state of the art*, such as changes to applicable standards and guidance documents, new information relating to the medical condition managed with the device and its natural course, medical alternatives available to the target population;”
Fundamental principles: IVDD

> IVDD Rec 3
  • this Directive lays down only such requirements as are necessary and sufficient to ensure, under *the best safety conditions*, free movement of the IVDs to which it applies;

> IVDD Rec 6
  • whereas the *essential requirements*, including requirements to minimise and reduce risks, should be applied with discretion, *taking into account the technology and practice at the time of design* and technical and economic considerations compatible with a *high level of protection of health and safety*;
Fundamental principles: IVDR

> **IVDR Rec 61**
  - To ensure a high level of safety and performance, demonstration of compliance with the general safety and performance requirements laid down in this Regulation should be based on clinical evidence.

> **IVDR Art 1(36)**
  - “Clinical benefit” means the positive impact of a device related to its function, such as that of screening, monitoring, diagnosis or aid to diagnosis of patients, or a positive impact on patient management or public health.

> **IVDR Rec 64**
  - It should be recognised that the concept of clinical benefit for IVDs is fundamentally different from that which applies in the case of pharmaceuticals or of therapeutic medical devices, since the benefit of IVDs lies in providing accurate medical information on patients, where appropriate, assessed against medical information obtained through the use of other diagnostic options and technologies, whereas the final clinical outcome for the patient is dependent on further diagnostic and/or therapeutic options which could be available.

> **Art 56 (3)**
  - 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 and that the device is safe.
Quiz 2

> How many times is “state of the art in medicine” noted in the IVDR?
Quiz 2

> How many times is “state of the art in medicine” noted in the IVDR?
  • Answer = 7

> How many times is clinical mentioned in the IVDD?
Quiz 2

> How many times is “state of the art in medicine” noted in the IVDR?
  • Answer = 7

> How many times is clinical mentioned in the IVDD?
  • Answer = 2

> How many times is clinical mentioned in the IVDR?
Quiz 2

> How many times is “state of the art in medicine” noted in the IVDR?
  • Answer = 7

> How many times is clinical mentioned in the IVDD?
  • Answer = 2

> How many times is clinical mentioned in the IVDR?
  • Answer = 209 (c.f. MDR = 678) Why the difference?

> What constitutes clinical evidence according to the IVDR?
Quiz 2

> How many times is “state of the art in medicine” noted in the IVDR?
  • Answer = 7

> How many times is clinical mentioned in the IVDD?
  • Answer = 2

> How many times is clinical mentioned in the IVDR?
  • Answer = 209 (c.f. MDR = 678) Why the difference?

> What constitutes clinical evidence according to the IVDR?
  Data based on:
  • Scientific validity
  • Analytical validity
  • Clinical validity
Establishing State of the Art in Medicine for an IVD

Clinical condition

Description Course Epidemiology Patient populations

Clinical question (diagnosis, prognosis, monitoring, screening, prediction, treatment options)

Clinical Options
Eg IVDs, radiology, symptoms

Steps

- Guidelines, standards, history
- Performance + safety options
- Advantages, disadvantages
- Benefit-risk profiles
- Unmet needs
Where do we find “state of the art” for IVDs

- Implementing acts and delegating acts
  - Harmonised standards
  - Common Specifications
  - EU Reference laboratory recommendations
  - MDCG guidance

- Activities of authorities (regulators, notified bodies, and HTA bodies such as NICE) and their related publications and recommendations, and outputs of market surveillance (e.g. ANSM, MHRA, MPIVDAOE, MAUDE, HPRA, EUDAMED… databases)

- Information on good clinical practice such as expert documents produced by professional medical associations, including clinical practice guidelines and consensus statements (e.g. ECVS)

- Reference materials and methods

- Publications (peer-reviewed journals)

- EQAS/proficiency testing
## Demonstration of clinical evidence

<table>
<thead>
<tr>
<th>Scientific Validity</th>
<th>Analytical Performance</th>
<th>Clinical Performance</th>
</tr>
</thead>
<tbody>
<tr>
<td>• What is the evidence for the association between the analyte and the clinical condition?</td>
<td>• How good is the IVD at detecting the analyte?</td>
<td>• How good is the IVD at providing information correlated with the patient’s clinical condition?</td>
</tr>
</tbody>
</table>
### Demonstration of clinical evidence

<table>
<thead>
<tr>
<th>Scientific Validity</th>
<th>Analytical Performance</th>
<th>Clinical Performance</th>
</tr>
</thead>
<tbody>
<tr>
<td>• relevant information on devices measuring the same analyte;</td>
<td>• analytical sensitivity</td>
<td>• diagnostic sensitivity</td>
</tr>
<tr>
<td>• scientific (peer-reviewed) literature;</td>
<td>• analytical specificity</td>
<td>• diagnostic specificity</td>
</tr>
<tr>
<td>• consensus expert opinions/positions from relevant professional associations;</td>
<td>• trueness (bias)</td>
<td>• positive predictive value</td>
</tr>
<tr>
<td>• results from proof of concept studies;</td>
<td>• precision (repeatability and reproducibility)</td>
<td>• negative predictive value</td>
</tr>
<tr>
<td>• results from clinical performance studies.</td>
<td>• accuracy (resulting from trueness and precision)</td>
<td>• likelihood ratio</td>
</tr>
<tr>
<td></td>
<td>• limits of detection and quantitation</td>
<td>• expected values in normal and affected populations.</td>
</tr>
<tr>
<td></td>
<td>• measuring range</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• linearity</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• cut-off</td>
<td></td>
</tr>
</tbody>
</table>
Also new to the IVDR

**Risk Management**

> GSPR 4

- Risk management shall be understood as a *continuous* iterative process throughout the entire lifecycle of a device, requiring regular systematic updating.
- 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*.

**Performance Evaluation**

> Annex 13 (1)

- 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.
- As a general rule, the 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
- an indication and specification of parameters to be used to determine, based on the *state of the art in medicine*, the acceptability of the *benefit-risk ratio* for the intended purpose or purposes and for the analytical and clinical performance of the device
## Demonstration of clinical evidence

<table>
<thead>
<tr>
<th>Scientific Validity</th>
<th>Means to demonstrate</th>
<th>SOA can change?</th>
</tr>
</thead>
</table>
| • What is the evidence for the association between the analyte and the clinical condition? | • Scientific peer-reviewed literature  
• Consensus opinion (prof societies)  
• Proof of concept studies  
• Clinical performance studies | • YES |
**Demonstration of clinical evidence**

<table>
<thead>
<tr>
<th>Analytical Performance</th>
<th>Means to demonstrate</th>
<th>SOA can change?</th>
</tr>
</thead>
<tbody>
<tr>
<td>• How good is the IVD at detecting the analyte?</td>
<td>• always to be demonstrated on the basis of analytical performance studies (EN stds, CS, ref methods, materials)</td>
<td>• Yes</td>
</tr>
<tr>
<td></td>
<td>• In the absence of such approaches, a clinical performance study comparing performance of the novel device to the current clinical standard practice is required.</td>
<td></td>
</tr>
</tbody>
</table>
Demonstration of clinical evidence

<table>
<thead>
<tr>
<th>Clinical Performance</th>
<th>Means to demonstrate</th>
<th>SOA can change?</th>
</tr>
</thead>
</table>
| • How good is the IVD at providing information correlated with the patient’s clinical condition? | • Clinical performance studies  
• Scientific peer-reviewed literature  
• Published experience gained by routine diagnostic testing | • Yes |
Quiz 3
Name the culprit
Quiz 3
Name the culprit

Plasmodium falciparum

Rubella
## Clinical question: Diagnosis of malaria infection

### RDT assay detecting HRP2

<table>
<thead>
<tr>
<th>Scientific validity</th>
<th>HPR2 antigen is well established</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analytical performance</td>
<td>HRP2 is specific except in some RF pos patients with rheumatoid arthritis. Antigen levels are not directly correlated with parasite load</td>
</tr>
<tr>
<td>Clinical performance</td>
<td>Good diagnostic sensitivity, except when disease due to other species, or the falciparum has a HRP2 deficiency. Reduced diagnostic specificity due to persistence post infection.</td>
</tr>
<tr>
<td>Clinical evidence</td>
<td>Aid to diagnosis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Disease</th>
<th>Malaria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cause</td>
<td>Plasmodium spp</td>
</tr>
<tr>
<td>Diagnostic options</td>
<td>Blood film review, RDTs, PCR, Serology</td>
</tr>
<tr>
<td>Current state of the art in medicine</td>
<td>Blood film review</td>
</tr>
<tr>
<td>Future state of the art in medicine</td>
<td>PCR</td>
</tr>
</tbody>
</table>
Examples

Clinical question:
Pre-pregnancy screening for previous exposure to rubella

<table>
<thead>
<tr>
<th>Disease</th>
<th>Congenital rubella syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cause</td>
<td>Rubella in pregnancy</td>
</tr>
<tr>
<td>Current state of the art in medicine</td>
<td>Prevention by vaccination of all non immune women, therefore testing for past exposure required</td>
</tr>
<tr>
<td>Current state of the art in medicine</td>
<td>Detection of antibodies using serology; if less than 10 IU/mL vaccinate.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Quantitative rubella IgG EIA</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Scientific validity</td>
<td>Rubella IgG acknowledged as marker of past exposure. However, not all antibodies are protective.</td>
</tr>
<tr>
<td>Analytical performance</td>
<td>IS used to establish quantitative values,</td>
</tr>
<tr>
<td>Clinical performance</td>
<td>Relied on literature</td>
</tr>
<tr>
<td>Clinical evidence</td>
<td>????</td>
</tr>
</tbody>
</table>
NSF INTERNATIONAL

Perform ance Evaluati on

Intend ed use

Risk Assessme nt

PMS

PMS Report

GSPRs

State of the art
State of the art in medicine

Benefit

Risk

PMPF

Perf studies

Perfor mance Claims

PMS IFU

Intend ed use

Benefit

Risk

GSPRs

State of the art
State of the art in medicine
Open panel debate
Thank you for your attention

Gert Bos
Gert.Bos@Qservegroup.com