Demonstrating State of the Art for IVDs

Liz Harrison

Global Head, IVD

Ana Chiva

Senior Technical Specialist and Scheme Manager

10 Jun 2025

1 IVDR requirements for SotA

2 Definition of SotA

3 How to establish SotA

4 How to demonstrate SotA

5 Examples

6 Recap

IVDR requirements for State of the Art

"State of the Art *in medicine*" appears 4 times in the IVDR but is not included in Article 2 "Definitions".

PE Plan and PE Report

Annex XIII 1.1 (PE Plan)

Annex XIII 1.3.1 (PE Report)

Annex XIII 1.3.2 (PE Report)

Article 56 - PE & Clinical Evidence

The data and conclusions drawn from the assessment of those elements shall constitute the clinical evidence for the device. 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. The clinical evidence derived from the performance evaluation shall provide scientifically valid assurance, that the relevant general safety and performance requirements set out in Annex I, are fulfilled, under normal conditions of use.

IVDR requirements for State of the Art

“State of the Art” appears 15 other times throughout the IVDR and exists in various forms.

Most notably – Annex I, Chapter 1, Section 1

ANNEX I

GENERAL SAFETY AND PERFORMANCE REQUIREMENTS

CHAPTER I

GENERAL REQUIREMENTS

GSPR 1

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.

IVDR requirements for State of the Art

“State of the Art” appears 15 other times throughout the IVDR and exists in various forms.

Other references

CPSP, Annex XIII 2.3.2 (g & h)

PMPF Planning, Annex XIII, Part B, 5.2 (f)

EURLs – Article 100

GSPR 4

4. 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. To reduce risks, the manufacturers shall manage risks so that the residual risk associated with each hazard as well as the overall residual risk is judged acceptable. In selecting the most appropriate solutions, manufacturers shall, in the following order of priority:

Definition of State of the Art

“State of the art in medicine” versus “*Generally acknowledged state of the art”*.

In the context of IVDR, the two phrases are probably interchangeable.

MDCG 2021-5 Rev. 1 Section 3.5 discusses various definitions from different sources.

Informal BSI IVD interpretation: “*the generally accepted clinical use of a particular analyte or biomarker, with respect to the clinical condition(s) or physiological process(es) indicated by the device intended purpose and technology*”.

Definition of State of the Art

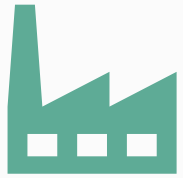
Does not mean the most technically advanced solution.

Technology choice is a trade off between analytical and clinical parameters, user costs, patient access etc.

Many technologies can be valid. All must meet definition of SotA.

E.g., clinical sensitivity may be lower but must still be within the clinically valid range.

Establishing the generally accepted use of an analyte / biomarker



As an IVD manufacturer, you should define this up front before developing your device.

Work with stakeholders to incorporate establishing SotA early in the design control process:

- Commercial
- Medical / clinical affairs
- Customer and user needs.

Different activities and levels of evidence may be required for:

- Established biomarkers
- Novel biomarkers
- Disruptive technologies.

Establishing the generally accepted use of an analyte / biomarker

Established biomarkers

European or International standards.

Clinical guidelines – ideally European.

Common Specifications.

Reference materials.

Peer-reviewed scientific literature.

Consensus expert opinions / positions from relevant professional associations.

Novel biomarkers or devices

Clinical guidelines – could be from another region.

SotA for current status quo.

Proof of concept studies.

Clinical performance studies.

Aim to build evidence - how does the novel biomarker / device perform versus current process.

Disruptive technologies

As the others.

Combined with RM and PMS.

Control the risk of changing the patient care pathway.

Establishing the generally accepted use of an analyte / biomarker

In all cases, combine demonstration of SotA with **risk management** and **post-market** activities.

Novel biomarkers / devices and disruptive technologies.

SotA is harder to prove pre-market.

Strong emphasis on risk management and PMS / PMPF.

Plan to identify if the device is causing harm.

Collect data to prove the device **is not** doing harm.

How to demonstrate State of the Art

Describe SotA in your **Performance Evaluation Plan** (Annex XIII 1.1 indent 7).

Document how you plan to show your device meets the SotA.

What does this mean **objectively** for your device?

- Sample type (including stability, storage conditions, endogenous and exogenous interferants).
- Common Specifications.
- Product specific standards e.g., ISO 15197.
- Certified Reference Materials.
- Measurement within the established clinical ranges and thresholds – LoD, LoQ etc.
- Required sensitivity and specificity.
- Inclusivity of the clinically relevant strains of an infectious agent.
- Identification of the clinically relevant mutations for a particular condition / CDx therapeutic decision.
- SW device yielding clinically relevant information for diagnostic decisions.

How to demonstrate State of the Art

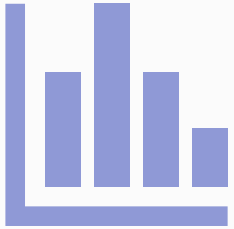
State of the art is loosely linked to Scientific Validity

- How is the analyte linked to a clinical condition or physiological state?
- How should it be measured and presented as clinically usable information?

Plan how you will show each element

- Analytical performance
- Clinical performance
  - Clinical performance studies
  - Scientific peer-reviewed literature
  - Published experience gained by routine diagnostic testing

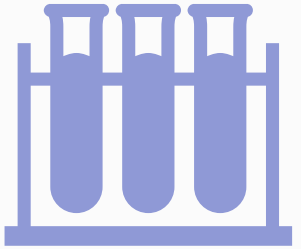
How to demonstrate State of the Art



Analytical Performance Studies

Some SotA elements can be demonstrated via Analytical Performance.

E.g., LoD, LoQ, measuring range, cut off, interference etc.



Clinical Performance Studies

SotA performance will nearly always need to be shown in Clinical samples.

E.g., Clinical Performance Studies (or other means of demonstrating CP per Annex XIII 1.2.3).

How to demonstrate State of the Art – established biomarkers

Is there an existing competitor device that already meets State of the Art?

Comparator Clinical Performance Study - show that your device has (at least) equal performance to the comparator device.

Plan ahead - how will you resolve discordant results? Which result will be regarded as “truth”?

Use of a third device for discordant result investigations?

Ensure technical documentation contains a description of why the comparator is SotA.

Why does equal performance mean your device is SotA? Is it CE marked?

How to demonstrate State of the Art – novel biomarkers

Define a composite reference method that is current State of the Art for the analyte being detected.

Clinical Performance Study comparing your device versus composite reference method.

Scientifically justify and plan how you will resolve discordant results – there could be many.

Which result will be regarded as “truth” and why?

RM and PMS / PMPF to control risks to patient. Does the benefit outweigh the risk?

How to demonstrate State of the Art

Annex XIII 1.3.2 requires a **Performance Evaluation Report** that includes:

"the clinical evidence as the acceptable performances against the state of the art in medicine."

Document how the State of the Art defined within the PE Plan has been met.

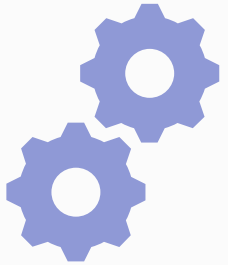
What objective evidence is there?

Add to SSP for Class C and Class D devices. Keep up-to-date.

How to demonstrate State of the Art

Annex XIII Part B 5.2(f) - the PMPF plan shall include:

"An evaluation of the performance data relating to equivalent or similar devices, and the current state of the art."



Plan how you will monitor changes to SotA

Have a system that allows this to input into PMS, Risk Management and updates to the PE Report via PMPF and/or PMS Reporting / PSUR.

Next webinar on 08 July will discuss this.

Examples

Health warning.

The following examples are simplified and describe a general approach.

They do not represent the full extent of expected Performance Evaluation, Risk Management and PMS activities.

Manufacturers responsibility to evaluate the full intended purpose, IVDR requirements, Common Specifications and harmonised ISO standards (EN ISO 13485, EN ISO 14971 etc.).

Example 1

Established biomarker in plasma, ELISA.

SotA easily accessible in scientific literature and clinical guidelines.

Units of measurement, linearity requirements, precision, reference materials, sample type and data analysis

PE Plan - clear definition of SotA.

Consider using a table detailing each element and how it will be objectively measured.

SotA demonstrated via analytical and clinical performance studies.

PE Report describes how each element of SotA is met and a clear conclusion. Consider using a table format.

Example 2

Novel biomarker in plasma, ELISA.

Current SotA clinical diagnosis is to detect other biomarkers in CSF.

Scientific validity and SotA for the novel biomarker can be established via scientific literature linking the biomarker to the clinical condition, proof-of-concept studies and a clinical performance study.

SotA demonstrated via clinical performance study.

Show similar diagnostic performance as the analyte in CSF with paired plasma samples.

Benefit risk ratio impacted favourably - plasma is a less invasive sample than CSF.

Example 3

Oncology CDx mutations, single gene target, FFPE biopsy sample, PCR assay.

Current SotA identifies 5 well characterised SNPs for a CDx call.

Additional 3 SNPs with emerging scientific validity.

5 SNPs: SotA easily accesible via ESMO clinical guidelines and INN EPAR.

3 SNPs: SotA established via scientific literature with discussion about benefit : risk of reporting these mutations.

5 SNPs: SotA demonstrated via clinical performance comparator study using a well-established CDx PCR test.

3 SNPs: SotA demonstrated via comparison with NGS data in the same clinical samples.

Benefit : risk favourable to report on the 3 SNPs with tentative scientific validity.

PMPF planned to monitor scientific validity and SotA of the 3 SNPs.

Example 4

Software algorithm. Combines output from multiple IVDs measuring physiological markers with patient age, weight, medical history. Provides a risk score for developing a specific disease.

Current SotA uses the same physiological markers individually combined to diagnose the disease.

Peer-reviewed literature shows strong evidence that age, weight and medical history are predictive risk factors.

SotA for the physiological markers is well established in clinical guidelines.

PE Plan discusses guidelines and peer-reviewed literature used to develop the algorithm for the risk score.

SotA demonstrated via clinical performance study showing that the same patients are identified by the algorithm as by the medical professional.

PMPF and RM used to manage the likelihood that the SW algorithm will identify at-risk patients earlier than existing SotA.

Example 5

HIV PCR diagnosis.

Current SotA is well established in clinical guidelines and literature identifies which HIV strains should be detected and how.

Common Specification has detailed performance requirements including numbers of samples to be tested.

SotA demonstrated via clinical performance comparator study and studies to meet CS requirements.

Discordant results resolved using a third SotA CE marked assay.

PMPF includes comprehensively planned regular bio surveillance activities.

Recap – definition of State of the Art for IVDs

Informal BSI IVD interpretation:

The generally accepted clinical use of a particular analyte or biomarker, with respect to the clinical condition(s) or physiological process(es) indicated by the device intended purpose and technology.

Recap – how to demonstrate State of the Art for IVDs

Pre-market phase

PE Plan

Establish SotA and document within PE Plan, including stages of PE that will be used to demonstrate each element (e.g., Analytical Performance, Clinical Performance)

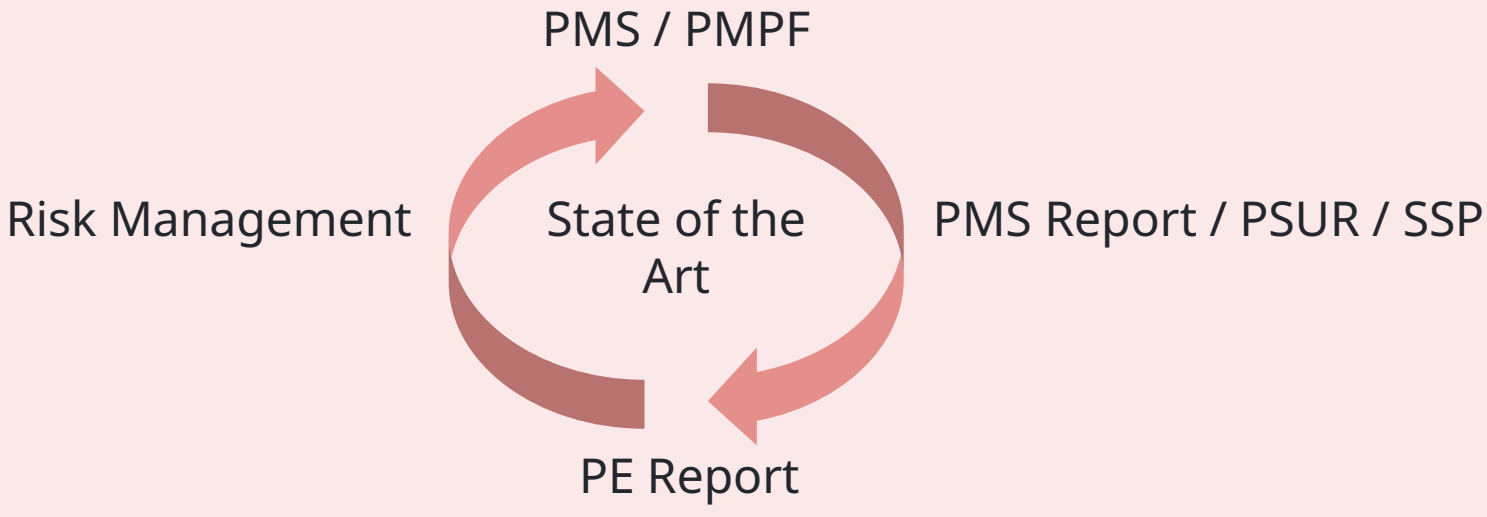
Execute PE Plan

Evaluate if data meets SotA goals. Update Risk Management documents and PMS / PMPF plans.

PE Report

Document within PE Report how the evidence meets SotA.

Post-market phase



Thank you – questions?

BSI Group

389 Chiswick High Road

London, W4 4AL

+44 345 080 9000

bsigroup.com