

GSPRs (GENERAL SAFETY AND PERFORMANCE REQUIREMENTS) THE HEART OF THE EU IVDR



INTRODUCTION

The heart of the European Union (EU) regulation of in vitro diagnostic medical devices (IVDs) lies in allowing market access to IVDs that offer clinical benefit, and are safe to the patient, the user of the IVD and others (such as service technicians). The regulation is written so that requirements ensuring a high level of protection of health and safety are, where appropriate, fulfilled.

Under the EU IVD Directive 98/79/EC, manufacturers have been required to comply with the essential requirements (ERs).

Now that new regulation has been introduced (EU IVD Regulation 746/2017), these requirements are expanded. Manufacturers must now demonstrate compliance with the general safety and performance requirements, the GSPRs, that provide broad, high-level criteria for safety and performance applicable to design, production, and post-production aspects, throughout the lifecycle of all IVDs.

Manufacturers that have demonstrated compliance under the Directive need to ensure that the IVD remains in conformity with the new legislation. To assist, NSF has developed a tool to compare the essential requirements (ERs) described in the EU IVD Directive with the general safety and performance requirements described in the new EU IVD regulation. (http://www.nsf.org/newsroom_pdf/md_wp_ivdr.pdf)

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.

The GSPRs are identified in Annex I of the EU IVDR. Like GSPR 1, the majority of the requirements are principle-based, ensuring that, as state of the art changes, a manufacturer considers if the IVD remains in compliance.

The GSPRs are divided into three major groups:

- > GSPRs 1 to 8 are found in Chapter One of Annex I, General Requirements. These GSPRs apply to all IVDs.
- > Chapter 2, Requirements Regarding Performance, Design and Manufacture, provides a list of GSPRs 10 to 19, where each GSPR must be considered for its applicability.



- > Chapter 3, Requirements Regarding Information Supplied With the Device, the ultimate chapter of this Annex, is dedicated to one overarching requirement applicable to labels and instructions for use. Within this one GSPR, there are many sub-requirements. Most will apply.

OVERVIEW OF THE GSPRs

Chapter I: General Requirements

General requirements defined in this chapter include:

- > The IVD should be suitable for its intended purpose during normal conditions of use and shall not compromise health and safety of users or where applicable, other persons.
- > Risks associated with the device should be reduced as far as possible without adversely affecting the risk-benefit ratio.
- > Manufacturers shall establish, implement, document and maintain a risk management system. A risk management plan shall be provided for each device.
- > Risk control measures for both overall residual risks and residual risk associated with each hazard 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.
- > Design and construction of IVDs must conform to safety principles with respect to patients and users and the risks relating to use error.
- > When used and maintained as intended, the characteristics and performance of a device shall not be adversely affected.
- > Medical devices are not to be adversely affected by transport or storage.
- > Benefits of IVDs should outweigh any known and foreseeable risks and any undesirable effects during normal conditions of use.

Chapter II: Requirements Regarding Performance, Design and Manufacture

Chapter II defines requirements around the following aspects of IVDs:

- > Performance characteristics
- > Chemical, physical and biological properties
- > Infection and microbial contamination
- > Devices incorporating material of biological origin
- > Construction and interaction with the environment
- > Devices with a measuring function
- > Protection against radiation
- > Electronic programmable systems — devices that incorporate electronic programmable systems and software that are devices in themselves
- > Devices connected to or equipped with an energy source
- > Protection against mechanical and thermal risks
- > Protection against the risks posed by devices intended for self-testing or near-patient testing



Chapter III: Requirements Regarding Information Supplied With the Device

This chapter focuses primarily on labels and instructions for use:

- > General requirements regarding the information supplied by the manufacturer
- > Information on the label
- > Information on the packaging of sterile devices
- > Information in the instructions for use

A MANUFACTURER'S RESPONSIBILITIES REGARDING GSPRs

The manufacturer is required to identify all GSPRs that are relevant to its device and then provide a justification if it thinks a particular GSPR is not applicable. Risk classification of the IVD does not influence the choice of GSPRs. From the lowest to the highest risk, it is important that a manufacturer has a mechanism within its quality management system (QMS) to ensure that all applicable GSPRs are identified and monitored for compliance. The QMS should also ensure that there has been sufficient rigor in identifying the most appropriate means to fulfill each relevant GSPR.

Depending on the IVD, some of the GSPRs of safety and performance will not apply. For instance, GSPRs relating to electrical safety (17.1, 17.2, 17.3, 17.4 and 17.5) do not apply to a rapid diagnostic assay that only involves lateral flow technologies and has no associated electrical equipment. In such cases, justification provided for the exclusion of all these GSPRs will include a statement that no electrical equipment or power is required for the functioning of the rapid assay.

ERs VS. GSPRs

Although a number of the GSPRs are the same as the essential requirements, many are new, and some have increased stringency. Even when the GSPR is the same, the emphasis in European law on "state of the art" (both for medicine and for technology) means that what constitutes conformity at one point in time may not apply later on. There is a need to constantly review the evidence held to support each GSPR, taking into account

the current state of knowledge in Europe regarding the device and its use.

NSF has developed a tool to easily compare the GSPRs of the IVDR and the essential requirements of the IVD Directive. Follow the instructions at the end of this white paper to download the tool.

WAYS TO DEMONSTRATE CONFORMITY WITH THE GSPRs

A checklist that manufacturers may complete to demonstrate how they have complied with the GSPRs for an IVD, and where the associated evidence can be found, is available from NSF (see end of paper). Evidence to demonstrate that a relevant GSPR has been met should be compiled after design lock-down has occurred, unless it can otherwise be justified.

Manufacturers can demonstrate that the GSPRs have been met for an IVD in many ways. Some examples include:

- > A documented and detailed risk analysis
- > Clinical evidence, compiled from the results of performance evaluation (the scientific validity of the marker to the clinical indications, the analytical performance and the clinical performance) as well as evidence of stability, robustness and usability of the IVD. More on clinical evidence later in this paper.
- > Literature searches and post-market experience
- > Copies of the label, packaging and instructions for use to demonstrate that information requirements have been met
- > Expert opinion, including that from relevant medical professional societies, national health technology assessment bodies such as NICE in the UK, etc.
- > References to production process controls as a source of evidence, for example, where the IVD has a measuring function, it is a requirement that it is accurate and reliable. This will usually involve calibration against an appropriate reference standard.



- > Relevant certification, for example a Certificate of Suitability to the European Pharmacopoeia, used as evidence that a material of biological origin has been sourced from herds certified as free from transmissible spongiform encephalitis (TSE). This can be used in support of GSPR 12. Other certificates may provide, for instance, evidence of calibration against reference materials.

This information then must be stored and appropriately referenced in the technical documentation, to have available for your notified body or a competent authority. Where standards have been used as a means to demonstrate conformity, the version of the standard used should be identified. Changes to standards may affect the ongoing state of conformity.

Your quality system should provide a mechanism to ensure that the evidence supporting each GSPR is reviewed at appropriate intervals. Prompts for review may come from change to the design or components/ formulation, post-market surveillance, changes to standards, and changes to current expert opinion.

Consequently, the manufacturer may need to update the risk assessment of the device to account for the impact of such changes and advances in knowledge.

Clinical Evidence

The manufacturer shall specify and justify the level of the clinical evidence necessary to demonstrate conformity with the relevant general safety and performance requirements. That level of clinical evidence shall be appropriate in view of the characteristics of the device and its intended purpose. It shall also reflect state of the art of the medicine.

Standards

The most common way to demonstrate compliance with the GSPRs is to meet a harmonised standard, or a similar standard. If the manufacturer chooses to use voluntary standards other than those recognised (the harmonised standards), it must provide evidence that the chosen standard is applicable to the manufacturer's quality system and that its application satisfies the requirements of the regulation. The use of such standards is not mandatory.

As discussed earlier, there is a requirement with a number of GSPRs to have evidence of the IVD being generally acknowledged as state of the art. Published standards for IVDs are developed through a process of consensus, and therefore are usually accepted to reflect the generally acknowledged state of the art. This is why standards need to be considered by a manufacturer, even though compliance with any given standard is not compulsory.

An update or change to a standard should trigger the manufacturer to undertake a risk assessment of complying or not complying with the latest standard or version. The outcome of the risk assessment will help inform the decision of whether to apply the change. If the manufacturer decides to:

- > Update to the latest version of the standard, it is important to prepare a risk-based plan that outlines how and when compliance with the standard will be achieved
- > Not update to the latest version of the standard, the manufacturer must hold justification for not complying and have relevant evidence that a GSPR is still fulfilled.

When choosing which standards to apply to each device, manufacturers should take into consideration the:

- > Intended purpose of the device
- > Environment in which it is likely to be used
- > Likely users of the device
- > Generally acknowledged state of the art in technology and medicine

Standards that are commonly used by IVD manufacturers are:

- > EN ISO 14971—Application of risk management to medical devices
- > EN ISO 13485—Quality management systems: Requirements for regulatory purposes
- > EN ISO 60601—Medical electrical equipment
- > EN ISO 18113 (1-5) In vitro diagnostic medical devices — Information supplied by the manufacturer (labelling)



- > EN ISO 23640:2015 In vitro diagnostic medical devices — Evaluation of stability of in vitro diagnostic reagents
- > EN ISO 15223-1:2016 Medical devices — Symbols to be used with medical device labels, labelling and information to be supplied — Part 1: General requirements
- > IEC 60601: a family of standards relating to the safety and performance of medical electrical equipment
- > IEC 62304: Medical device software—Software life cycle processes
- > CLSI EP 5A2 Evaluation of Precision Performance of Quantitative Measurement Methods; Approved Guideline—Second Edition

If a standard is used in showing compliance with a GSPR, the manufacturer should include in the technical file for the IVD:

- > Identification of the standards used, including the version/year
- > For each standard used, a statement:
 - Of the requirements in the standard that are met with reference to the corroborating evidence in the technical documentation
 - Whether any of the requirements are non-applicable and the justification of the same
 - Whether any deviations from the standard were made, and justification of the same
 - Including information on any ways in which the standard may have been adapted for application to the particular device (for example, if alternative tests or statistical analysis are allowed, which of these are performed in relation to that device)

Note: At time of publication, no standards have been identified as harmonised according to the IVDR. Relevancy of EN standards considered harmonised to the IVDD must be determined by reference to the new regulation.

Common Specifications

In areas where no harmonised standards exist or where they are insufficient, the Commission may lay down common specifications that provide a means of complying with the general safety and performance requirements. Common specifications provide the requirements for performance studies and performance evaluation and/or post-market follow-up, laid down in the new Regulation.

Where a relevant common specification exists, a manufacturer is compelled to undertake testing in accordance with these specification as a means of demonstrating fulfillment of certain GSPRs. Exceptionally, a justification is required if they have not been observed, with valid reasoning that the adopted solutions still ensure a level of safety and performance that is at least equivalent thereto.

GSPR Q+A

What's a good example of compliance with a GSPR?

GSPR 9.2 states: “The performance characteristics of the device shall be maintained during the lifetime of the device as indicated by the manufacturer.” This GSPR relates to the stability of the IVD, when stored and/or used, according to claimed conditions that typically include time and temperature and may also state humidity and light. Stability claims should be made for the IVD when stored unopened, when opened and in use, and if used on an instrument, for conditions on board. The manufacturer should also know what transport conditions the IVD can tolerate and yet still maintain shelf life and in-use stability claims.

The most useful way to prove that the product will remain stable as claimed is to use methods proposed in standards. EN ISO 23640:2015 and CLSI EP25A provide clear methodologies and if followed, claims for stability, supported by evidence generated from implementation of these standards, will give evidence of conformity to GSPR 9.2.



I am trying to meet the GSPRs of my IVD which is also considered a machine under Directive 2006/42/EC. What legislation has the priority?

Where an IVD is also captured as machinery under this Directive, a manufacturer shall, where a hazard

relevant under the machinery Directive exists, also meet the essential health and safety requirements set out in Annex I to that Directive to the extent to which those requirements are more specific than the general safety and performance requirements set out in Chapter II of Annex I to the EU IVD Regulation.

I believe my laboratory will be eligible for a health institution exemption. Does my in-house developed test (some refer to this as a laboratory-developed test) have to meet the GSPRs?

The relevant GSPRs are the requirements that must be complied with even if your institution is given an exemption. All other requirements of the IVDR are

exempt, provided that your IVD is used only within your health institution, and all other conditions laid out in Article 5, Section 5 of the EU IVD Regulation are met.

FINAL WORDS

There are many important aspects requiring attention when it comes to meeting the new IVDR safety and performance requirements:

- > Even if you believe you have evidence under the IVDD, this is not sufficient. Evidence for all relevant GSPRs must be available. Download the NSF tool for help.

- > Evidence at one point in time may no longer support state of the art of the technology or state of the art of medicine.
- > Remember this is EU law, aimed at protecting residents in Europe. Evidence sourced from other jurisdictions may not provide sufficient proof of conformity.
- > Evidence to support each GSPR for the IVDR may not be sufficient to cover other regulations applicable to a device,
- > A well-executed, proactive post-market surveillance system is not only required under the regulation but can also provide you with much needed evidence to support your GSPRs. Passive surveillance mechanisms for IVDs rarely work, given that the impact of a false result does not do direct harm to the patient. Reach out to your users – you should!
- > NSF can assist you with meeting the GSPRs. We have experts in IVDs, quality and manufacturing technologies as well as training modules available to assist.

NSF INTERNATIONAL

789 N. Dixboro Road, Ann Arbor, MI 48105, USA | **T** +1 (202) 822 1850

The Georgian House, 22/24 West End, Kirkbymoorside, York, UK YO62 6AF | **T** +44 (0) 1751 432 999

Beim Strohhause 17, 20097 Hamburg | **T** +49 40 66 87 88 -100

E healthsciences@nsf.org | www.nsfhealthsciences.org | Follow us on   