IVD-R Annex I Global Safety and Performances Requirements (GSPR). A New Set of Requirements for Clinical Laboratories Performing Laboratory Developed Tests

B. Ezzouaouy | Senior Product Manager | Beckman Coulter Life Sciences

IN THIS PAPER YOU WILL

- Understand the importance of the Annex I GSPR for clinical laboratories performing flow cytometry Laboratory Developed Tests, in the context of the new EU IVD-R 2017/746 Regulation
- Learn more about the requirements listed in the Annex I GSP
- Learn more about the implications of these requirements for clinical laboratories

Introduction

The new European In Vitro Diagnostic (IVD) Regulation 2017/746 (IVD-R) replaces the In vitro diagnostics Directive (98/79/EC) (IVD-D) which has been regulating IVD products since its first publication in 1993. The IVD-R entered in force in May 2017, and the different stakeholders have until May 2022 to be compliant, with a 5-year transition period. Compared to the IVD-D, the IVD-R raise the bar significantly higher for IVD manufacturers to be compliant, with additional requirements including but not limited to the implication of notified bodies, implementation of pro-active post-market surveillance processes and additional requirements for performances and clinical evidence demonstration.

The IVD-R does not only raise the bar higher for manufacturers, but for the complete IVD ecosystem including clinical laboratories who were not affected by the IVD-D but are in the scope of IVD-R. Clinical laboratories will indeed need to be compliant with IVD-R for the IVD assays they develop and manufacture within their laboratories, often called Laboratory Developed Tests (LDTs). While the IVD-R acknowledges the need for LDTs to diagnose specific pathologies, as there are no CE-marked and commercially available assays for all disease areas, it also understands the risk associated with under controlled, high-risk LDTs. The IVD-R objective to further improve the quality, safety and reliability of IVD products would not have been achieved if the requirements would have been increased only for manufacturers, while individual laboratories would still have the flexibility to develop their own home-brew assays with significantly less requirements.

The IVD-R provides for LDTs a partial exemption from the requirements of the regulation as long as the labs meet the conditions listed in article 5.5.

Table 1: IVD-R Article 5.5 Requirements

a. The devices are not transferred to another legal entity;
b. Manufacture and use of the devices occur under appropriate quality management systems;
c. The laboratory of the health institution is compliant with standard EN ISO 15189 or where applicable national provisions, including national provisions regarding accreditation;
d. The health institution justifies in its documentation that the target patient group's specific needs cannot be met, or cannot be met at the appropriate level of performance by an equivalent device available on the market;
e. The health institution provides information upon request on the use of such devices to its competent authority, which shall include a justification of their manufacturing, modification and use;
f. The health institution draws up a declaration which it shall make publicly available, including: (i) the name and address of the manufacturing health institution, (ii) the details necessary to identify the devices, (iii) a declaration that the devices meet the general safety and performance requirements set out in Annex I to this Regulation and, where applicable, information on which requirements are not fully met with a reasoned justification therefor;
g. As regards class D devices in accordance with the rules set out in Annex VIII, the health institution draws up documentation that makes it possible to have an understanding of the manufacturing facility, the manufacturing process, the design and performance data of the devices, including the intended purpose, and that is sufficiently detailed to enable the competent authority to ascertain that the general safety and performance requirements set out in Annex I to this Regulation are met. Member States may apply this provision also to class A, B or C devices in accordance with the rules set out in Annex VIII;
h. The health institution takes all necessary measures to ensure that all devices are manufactured in accordance with the documentation referred to in point (g);
i. The health institution reviews experience gained from clinical use of the devices and takes all necessary corrective actions.

LDTs fulfilling these conditions only need to comply with Annex I General Safety and Performance Requirements (GSPR). Therefore the GSPR listed in the IVD-R Annex I will be, with article 5.5 requirements, the cornerstone for clinical laboratories to be compliant with the IVD-R for their laboratory developed tests. Compliance with the GSPR is far from straightforward, and any lab planning to perform LDTs after May 2022 should carefully analyze the GSPR requirements, and plan significantly upfront their implementation to ensure they are ready by the deadline. To be noted that there are no grandfathering for LDTs with IVD-R, even LDTs which have been used for years will have to meet the article 5.5 conditions including Annex I GSPRs to continue being used after May 2022.

Overview of Annex I Global Safety and Performances Requirements (GSPR)

Before being considered acceptable for use per the IVD-R requirements, IVD devices including LDTs must be safe and achieve their intended purpose in terms of performance requirements. There are 20 General Safety and Performance Requirements for in vitro diagnostic devices listed in Annex I of the IVD-R. These requirements are the foundation of the regulation. IVD manufacturers, and clinical laboratories performing LDTs, should demonstrate conformity with these GSPRs by referencing to harmonized standards or internal procedures. The GSPRs are divided into 3 chapters:

- Chapter I – General requirements
- Chapter II – Requirements regarding performance, design and manufacture

- Chapter III – Requirements regarding the information supplied with the device

This document provides a high level overview of the GSPRs included in these 3 chapters.

Chapter I – General requirements

This chapter is mostly related to risk management and risk/benefit ratio. While this is already an area of focus and expertise for IVD manufacturers, most clinical laboratories are less experienced with such requirements and will have to deepen their expertise and establish new processes. Chapter I includes 8 GSPRs which apply to all IVDs covering the following aspects:

1. Device performances suitability with its intended purpose, without compromising health and safety of users or where applicable, other persons

2. Identification and reduction, as far as possible, of the risks associated with the use of the device, without adversely affecting the risk-benefit ratio

3. Definition, implementation and documentation of a risk management system updated continuously through the life cycle of the device

4. Risk control measures adopted for both the design and manufacturing of the devices aiming to reduce overall residual risks as well as residual risks associated with each hazard. Manufacturers shall inform users of any residual risks.

5. Considerations related to the elimination or reduction of risks related to use error

6. Ensuring that when used and maintained as intended, characteristics and performances of the device are not adversely affected

7. Design, manufacturing and packaging of devices to ensure they are not adversely affected during transport or storage

8. Considerations of the benefits versus risks of the device

Chapter II – Requirements regarding design and manufacture

The second chapter list requirements which are probably the ones clinical laboratories will be the most familiar with, in particular laboratories with robust assay validation processes, such as ISO 15189 accredited labs. It defines 11 requirements covering the following areas:

1. Performance characteristics, including analytical performances (such as analytical sensitivity, specificity, repeatability, reproducibility, trueness/bias, accuracy, linearity, limit of detection and quantification…) and clinical performances (such as diagnostic sensitivity, specificity, expected values, positive and negative predictive values…) which should be maintained during the life time of the device

2. Chemical, physical and biological properties

3. Infection and microbial contamination

4. Considerations specific to devices incorporating materials of biological origin

5. Construction and interaction with the environment, including requirements for devices intended to be used with other devices (e.g. conjugated antibodies mixed in panels for flow cytometry analysis)

6. Considerations specific to devices with a measuring function

7. Protection against radiation

8. Considerations specific to devices that incorporate electronic programmable systems and software that are devices in themselves. These requirements may apply to laboratories using "home-made" algorithms for data analysis or use softwares which have not been validated by the manufacturer for use with the LDT

9. Considerations specific to devices connected to or equipped with an energy source

10. Protection against mechanical and thermal risks

11. Protection against the risks posed by devices intended for self-testing or near-patient testing

Chapter III – Requirements regarding the information supplied with the device

The third and last chapter of the IVD-R Annex I focuses primarily on labels and instructions for use, with one GSPR divided onto 4 parts:

1. Label and instructions for use:

    1.1. General requirements regarding the information supplied by the manufacturer, including but not limited to information related to labelling, instruction for use and residual risk communication

    1.2. Information on the label: comprehensive list of information to be displayed on devices labelling, divided into 20 different categories

    1.3. Information specific to the packaging of sterile devices

    1.4. Information in the instruction for use (34 elements listed)

Each laboratory performing LDTs will be responsible for identifying all GSPRs which are relevant to its LDT and justify why some requirements are not applicable. The Quality Management System (QMS) of the lab should adequately ensure that the evidence supporting each GSPR is updated as necessary, such as in the event of a design change (e.g. new conjugated antibody included in a panel, change in formulation) or following observations during post-market surveillance or changes to a standard or current expert opinion. While the initial implementation and compliance with IVD-R GSPR will be time and resources consuming for clinical laboratories performing LDTs, the efforts required for the sustainment will also be significant and should not be underestimated.

Discussion

The IVD-R undoubtedly increase complexity for IVD products, including LDTs, to be compliant. The level of complexity is probably comparable to the US FDA requirements for IVDs. Compliance with IVD-R will certainly be a challenge for IVD manufacturers but even though smallest companies may not have the resources and capabilities to raise the bar of their QMS, most manufacturers may have the expertise to fulfil these commitments, although this will require significant additional efforts. On the other hand, the core expertise of clinical laboratories is to produce diagnostic results, not to produce diagnostic assays, and the vast majority will not have the expertise and resources to be compliant with the full IVD-R. The article 5.5 provides an alternative if its requirements are met, though these require nonetheless significant efforts and compliance with the IVD-R Annex I GSPR will be a significant hurdle. This will discourage the use of LDTs when not absolutely necessary, given the additional efforts needed to implement and sustain the required QMS. In addition, the use of LDTs will decrease significantly given that the IVD-R also restrict their usage to tests used for specific needs of patient groups which cannot be met at the appropriate level of performance by an equivalent device available on the market, as specified in IVD-R article 5.5 d).

This is a revolution for most clinical laboratories, as LDTs often play a key role in particular for IVD disciplines such as flow cytometry. For instance, a case study recently published by a clinical lab in Belgium[1], showed that only 41.8% of laboratory tests in their institution were CE-IVD currently and there was no alternative on the market for 71.5% of the 537 LDTs they performed. Compliance with the IVDR will require a major investment of time and effort for these labs. In addition to the upfront investment in terms of time and resources to upgrade their QMS, labs should plan to ensure they have the capabilities to sustain the compliance, as all documents and processes will need to be updated through the life cycle of the device. Overall, the task is not facilitated by the lack of information and guidance available and the limited sections devoted to LDTs in the IVD-R.

While the IVD-R is implemented since May 2017, many clinical laboratories are either not aware of the implications for their operations, or lacking clarity and guidance documents on how to adjust their QMS to meet the new requirements. This is concerning given that IVD-R compliance is a journey requiring a significant upfront planning and the deadline for compliance is approaching rapidly. The IVD industry, through the voice of MedTech, also believes that some key elements are missing to make the IVD Regulation implementation workable, and has been raising concerns to the EU authorities[2]. Also LDTs are often used to improve workflows and/or reduce costs, which is not an acceptable justification according to IVD-R to not use a commercially available CE marked solution.

While the transition from IVD-D to IVD-R will be a significant journey for the IVD ecosystem, in fine it will result in higher quality IVD devices being used for diagnostic, be it commercially available products or LDTs, and will significantly lower risks toward patients.

References

1. The new IVD Regulation 2017/746: a case study at a large university hospital laboratory in Belgium demonstrates the need for clarification on the degrees of freedom laboratories have to use lab developed tests to improve patient care. Vermeersch et al. Clin Chem Lab Med July 2020

2. MedTech Europe urges EU authorities to make IVD Regulation implementation workable. July 2020. Press release. https://www.medtecheurope.org/news-and-events/press/medtech-europe-urges-eu-authorities-to-make-ivd-regulation-implementation-workable/

BECKMAN COULTER
Life Sciences

For Beckman Coulter's worldwide office locations and phone numbers, please visit "Contact Us" at **beckman.com**

FLOW-7861WP09.20