CHROMSYSTEMS

DIAGNOSTICS BY HPLC & LC-MS/MS

FACT SHEET

The In Vitro Diagnostic Regulation (IVDR)

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General Background

What is EU's in vitro diagnostics regulation (IVDR)?

The IVD Medical Device Regulation (IVDR 2017/746/EC) replaces the EU's directive on in vitro diagnostic medical devices (98/79/EC). As a European regulation, it will be effective in all EU member states and EFTA states immediately without the need to be transferred into law of respective states.

Published on May 5, 2017, with a 5-year transition period until May 2022, the regulation is now significantly more extensive and far ranging. IVD manufacturers are now scrambling to meet the product requirements of the new legislation. Many clinical laboratories are wondering what changes this will bring to the assays they have in use.

Impact for Clinical Laboratories

Does it also affect clinical laboratories?

IVDR is not only an issue for IVD-manufacturers, such as Chromsystems. The IVDR will have an impact on clinical laboratories as well. This is particularly true for medical laboratories that use their own "laboratory developed tests" (LDTs) and also affects clinical laboratories with accreditation (e.g. DAKKS or ISO 15189).

Laboratories producing their own in vitro diagnostic tests may not require a notified body for any product certification, but they would have to provide all evidence to their competent local authority. These laboratories must also have a quality management system –the ISO 15189 "accreditation" of laboratories is explicitly mentioned. Additionally, some information – such as a self-declaration – would be also required, and this declaration must state that the assay conforms with Appendix I of the IVDR.

What are the transition periods for Lab Developed Tests (LDTs)?

1. **Since May 26, 2022**
   - all LDTs in the EU must meet the general safety and performance requirements set out in Annex I of the IVDR, including the performance evaluation
   - all LDTs may not be provided to another legally independent facility

2. **From May 26, 2024**
   - Quality management system for IVD device development and manufacture must be in place
   - Quality assurance in the laboratory: ISO 15189 for quality assurance in the laboratory and compliance with national accreditation regulations
   - Provision of information to authorities on manufacturing, modification and use (upon request)
   - Public declaration of compliance with Annex I of the IVDR

As manufacturers need to bring all risk classes under the IVDR by latest May 2027, LDT labs were given a transitional period until May 2028 to review available tests and convert from LDT to CE-marked IVD if necessary.

Does that mean laboratories cannot use LDTs under IVDR anymore?

The IVDR includes one exemption that allows laboratories to manufacture, modify, and use LDTs on a non-industrial scale to meet the specific needs of target patient groups. This exemption, however, only applies to a small subset of LDTs. The regulation states:

"Health institutions should have the possibility of manufacturing, modifying and using devices in-house and thereby addressing, on a non-industrial scale, the specific needs of target patient groups which cannot be met at the appropriate level of performance by an equivalent device available on the market."

(Source: https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32017R0746&rid=6)

This means ...

If a similar or comparable CE-marked product is available on the market, which corresponds to the self-development in terms of performance level, the legal basis for the use of self-development in a clinical laboratory is no longer possible.

Most commercial laboratories will therefore be required to either switch to a CE-IVD assay, or alternatively, draw up a public declaration. This means that a clinical laboratory has to fulfil the same regulations as IVD-manufacturers and will need to fulfil the same standards and make the same efforts to the development of in-house developed tests – much like regular IVD manufacturers. This will be a large burden, as it will require them to meet several new standards, including compliance with the IVDR's Annex 1 "General Safety and Performance Requirements" and a quality management system framework. In many cases laboratories will need to consider the options of either making the effort to adapt their LDTs or switching to a commercial assay.

What are the benefits?

With in-depth verification and extensive monitoring the quality and safety of the products will ultimately increase. The added demands of the regulation will eventually benefit not only the market as a whole but also, more importantly, patients.

Impact for IVD Manufacturers

What will change in terms of the CE-IVD product certification?

In the past, manufacturers such as Chromsystems were able to self-declare around 90% of their CE-IVD products without certification by a notified body. This is going to change: self-certification will only be possible for class A products. In the future, manufacturers will have to supply the documentation for a CE-certification of assays risk class B or higher to the notified body (e.g. TÜV Süd), which will provide the CE-IVD certification after review. This also applies to products that already exist. Under the new regulation, every single Chromsystems assay needs to be re-certified in line with the new IVDR by the notified body (using the required documentation). Manufacturers are currently facing highly increased regulatory, personnel and financial challenges for implementing the required regulations.

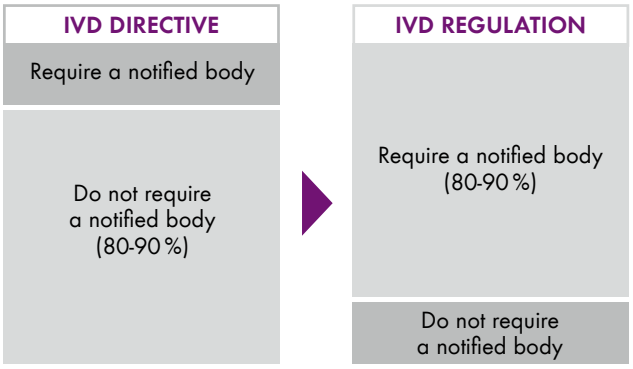

Fig. 1: While previously 90% of all IVDs were CE self-declared, and no notified body was involved, the landscape has changed with the new regulation.

Why does it require more documentation?

One new key component of IVDR is the clinical evidence, an area in which the old regulation had comparatively few requirements. In scenarios where a patient's treatment decision is made based on an IVD product, it is understandable that the legislators took action, and that the intended use of a kit now has to be clearly defined. The clinical evidence rests on three pillars: scientific validity, analytical performance and clinical performance (see fig. 2).

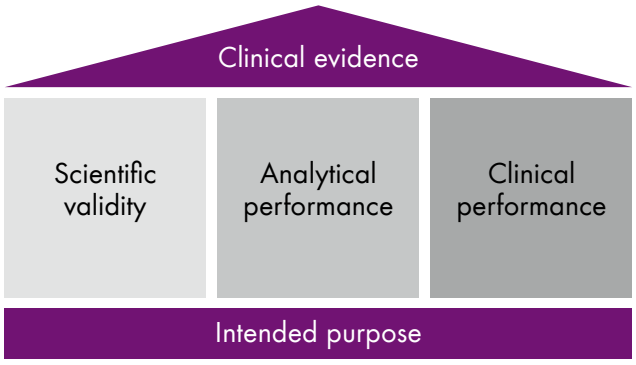

Fig. 2: The clinical evidence is made up of three components: scientific validity as well as analytical and clinical performance.

For scientific validity manufacturers need to present a considerable amount of documentation to the notified body, with evidence on the plausibility of the test: when is it making sense to determine a certain parameter? Can I use it to diagnose diseases? If so, which ones? Is it making sense to carry out therapeutic drug monitoring (TDM) for a certain drug and what evidence can I as a manufacturer provide for this? This pillar of scientific validity includes a consideration of the state of the art: is it recognised clinical standard practice to use the analyte in question to diagnose a certain disease?

For some parameters, this is easy because there is already a wealth of scientific literature available and the test is well established in the clinical environment. For example, the analysis of biogenic amines in diagnosing tumours is documented by a multitude of studies. In other cases, such as for metabolic disorders, it is different. If it is possible to determine more than 40 amino acids with one assay, the scientific validity and state of the art for each analyte and, in some cases, multiple metabolic disorders per analyte mentioned in the intended purpose, need to be proved by the manufacturer. Furthermore, clinical performance data of such assays can be elaborate due to the large number of clinical indications.

What happens if there are no studies available?

When there are no studies available in the scientific literature, and if a retrospective view of existing data and clinical pictures related to this is insufficient, then the manufacturers must carry out these studies themselves to provide the required evidence. In some cases, this can be extremely time-consuming and can lead to unacceptably high financial costs. In the long term, it will generally lead to higher quality of IVDs, but is likely to lead to a reduction in the variety of IVDs.

What are the timelines for manufacturers under IVDR?

New or modified products

All products developed and brought into market from May 2022 onwards as well as assays with significant changes must be compliant with the IVDR. This is independent of the product risk class.

Existing products *(so-called IVDD "legacy-devices")*

In the beginning of 2022, new transitional periods (Regulation 2022/112/EU) were announced for existing products, which depend on the classification of the product (see fig. 3). For Chromsystems, most products will fall in the IVDR risk classes B and C. All class B products will have to be IVDR–products by May 2027, all class C products by May 2026. An exception applies to products that already had a notified body certificate under the IVDD, such as newborn screening assays for the determination of phenylketonuria. In this case a transitional period until May 2025 applies.

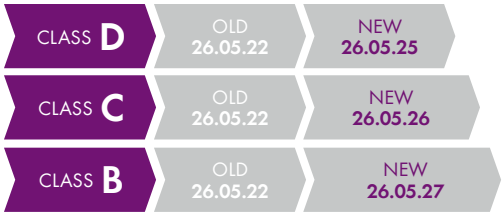

Fig. 3: Transitional periods of Class B to Class D products.

Products distributed by Chromsystems to laboratories prior to these deadlines may continue to be used legally until their expiration date is reached (Regulation 2023/607).

Is Chromsystems IVDR certified?

Yes, Chromsystems was certified by its notified body to have introduced, documented and implemented a quality management system pursuant to Regulation (EU) 2017/746 on in vitro diagnostic medical devices, Annex IX, Chapters I and III (Class C and B devices excluding self/near-patient-testing and companion diagnostics).

Discover our IVDR certified products here:

Resources:
https://eur-lex.europa.eu/legal-content/EN/TXT/HTML/?uri=CELEX:32017R0746
https://www.johner-institute.com/articles/regulatory-affairs/and-more/laboratory-developed-tests/

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Management system certified according to ISO 13485 (including MDSAP)

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