

IN-HOUSE DEVICE RESTRICTIONS OF USE

IN EUROPE IN THE LC-MS FIELD



Summary

In May 2022, the new In Vitro Diagnostic Regulation (IVDR) came into full force in the European Union (EU) replacing the old IVD Directive 98/79/EC (IVDD).

The new regulation aims to establish a robust and transparent regulatory framework for in vitro diagnostic medical devices (IVDs) to ensure patient safety while supporting innovation. Based on information available to Qarad, around 40 to 50% of the type of tests EU health institutions use are developed in-house or adapted from commercially available tests or kits, however, they mostly represent specialty diagnostics because around 95% of the volume of assays used in EU health institutions are made with IVD approved devices.

Although the IVDR outlines some partial exemptions for European health institutions using in-house assays (also known as Laboratory Developed Tests - LDTs or In-House Devices - IHD), there is still uncertainty around the interpretation of the new regulations in this field. This whitepaper looks at the implications of the IVDR for Liquid Chromatography-Mass Spectrometry (LC-MS) test kits and instrumentation, focusing on areas of flexibility for laboratories to integrate general laboratory equipment with IVDR-compliant products.

Introduction

In late May 2022, the European market brought in a new Regulation for IVDs to replace the previous IVDD. The new Regulation revises a Directive that was some 25 years old and expands its scope. In-House Devices (IHD) were not regulated by the IVDD, but although the IVDR exempts IH-IVDs from some of the requirements applicable to CE-marked devices, this exemption comes with conditions and, for the first time, sets out clear and compulsory harmonized requirements for IVDs manufactured and used within a health institution.

Health institution has been defined by the IVDR in Art. 2(29) as:



‘health institution’ means an organisation the primary purpose of which is the care or treatment of patients or the promotion of public health;”

Although not specified, the interpretation is that European private laboratories do fall in such definition.

The new EU IVDR is intended to:



...establish a robust, transparent, predictable and sustainable regulatory framework for in vitro diagnostic medical devices which ensures a high level of safety and health whilst supporting innovation.

The importance of “supporting innovation” within health institutions was demonstrated during the COVID-19 pandemic, where rapidly developed clinical PCR-based tests for SARS-CoV-2 variants were the prototypes for commercialized tests adopted globally.

The IVDR thus needs to balance setting high standards of quality and safety for IVDs, while supporting the small and medium-sized academic and commercial enterprises active in this sector.

Responsibility for IVDR compliance is assigned to the test “manufacturer”, however, acknowledging their essential role in developing novel diagnostics, the IVDR includes partial exemptions for health institutions where there is no equivalent commercial IVD available. It states that:



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 that cannot be met at the appropriate level of performance by an equivalent device available on the market.

In such scenarios, responsibility for IH-IVDs is assigned to the health institution itself, under defined conditions. However, there is still a considerable grey area when it comes to integrating commercial kits and instruments for specific applications or indications where determining responsibility for IVDR compliance is less clear.

Clinical laboratories often embrace LC-MS for developing IH-IVDs, owing to its greater specificity, selectivity, and sensitivity compared with other technologies. In addition, LC-MS can offer greater productivity through its multi-channel LC capabilities.

These labs typically purchase their LC-MS instrument from an instrument manufacturer and their LC-MS analyte test kits from a separate test kit manufacturer. Yet, because the LC-MS business is not vertically integrated, there is typically no one-stop-shop or single vendor with responsibility for all the elements of the entire test system (test kit and LC-MS instrument) being compliant with IVDR.

Instructions for Use (IFU) provided by the LC-MS test kit manufacturer can state that such kit is IVDR compliant (thus can be officially used for IVD purposes) in two ways:

- Either when the kit is combined with specifically mentioned LC-MS instruments, by quoting their make and model (regardless of whether IVD-CE marked under the IVDD or IVDR, or classified as General Laboratory Equipment(GLE) or Research Use Only (RUO)) - or
- By specifying that such kit must be used on any LC-MS instrument provided that it has certain (& listed) technical features. Also in this case regardless of the regulatory classification of the instrument: RUO, GLE, IVD.

By making such claims, the manufacturer of the kit takes full responsibility that its kit, when combined with the LC-MS instruments as described above, fully complies with the IVDR for the intended purpose it has given to the kit.

It must be clear that in all other cases, European clinical laboratories will have to ensure IVDR compliance through the health institution exemption outlined in IVDR Article 5.5.

In this whitepaper, we look at the requirements of Article 5.5, when they will come into force and areas of flexibility for labs combining GLE/RUO instruments and products with commercial test kits and reagents.

What is the scope of IVDR?

When interpreting the implications of the new IVDR for IVD systems that integrate separate IVD devices (test kits and instruments), it is important to consider exactly how the new Regulation defines IVDs and to what the IVDR does and does not apply.

Products for general laboratory use (GLE) or research-use only (RUO) are out of scope, unless such products, in view of their characteristics, are specifically intended by their manufacturer to be used for in vitro diagnostic examination.

The new Regulation does apply to:

In vitro diagnostic medical devices and accessories for in vitro diagnostic medical devices (referred to as 'devices' throughout the Regulation) are in scope, and are defined as:



...any medical device which is a reagent, reagent product, calibrator, control material, kit, instrument, apparatus, piece of equipment, software, or system, whether used alone or in combination, intended by the manufacturer to be used in vitro for the examination of specimens, including blood and tissue donations, derived from the human body, solely or principally for the purpose of providing information on one or more of the following:

- a. A physiological or pathological process or state
- b. Congenital physical or mental impairments
- c. Predisposition to a medical condition or disease
- d. Determining the safety and compatibility with potential recipients
- e. Predicting treatment response or reactions
- f. Defining or monitoring therapeutic measures.

Although the definition of an IVD within the IVDR aligns with international consensus, it is notable that the Regulation does not specifically mention IHD at all, instead referring to 'devices manufactured and used only within health institutions established in the Union. However, an analysis of the Regulation suggests that all devices used for in vitro diagnostic medical purposes, alone or in combination, could be regarded as IHDs, based on three scenarios (Table 1) and all would be subject to Article 5.5.

Table 1. Qualification as an IHD according to three major scenarios.

IHD Scenario	Qualification
Scenario 1	An IVD assay created in the laboratory with non IVD-CE marked material: reagents, biological components etc. either produced by the lab or purchased on the market.
Scenario 2	Combination by the laboratory of IVD-CE-marked devices and non-IVD-CE-marked devices used for In Vitro Diagnostic purposes.
Scenario 3	Use by the laboratory of IVD CE-marked devices out of the scope (off-label use) of the manufacturer's product information (e.g., with regard to the used matrix volumes, intended purpose of use, dates of expiry, sample type, etc.). This scenario also includes the use by the laboratory of non-IVD CE marked devices (Research-Use Only, General Laboratory Products/Equipment, "For laboratory use only",) for In Vitro Diagnostic purposes.

The IVDR classifies IVDs into four classes, with increasing personal (individual) and public health potential risks from Class A to D (Table 2). Requirements for products developed by and used within health institutions to qualify for exemption from IVDR vary depending on the class of IVD.

Table 2. IVD classification under IVDR

Classification	Example of the intended purpose of the device (non-exhaustive)
Class A	<p>(Low individual and public health risk)</p> <ul style="list-style-type: none">• Products/instruments for general laboratory use (e.g., buffers, culture media, and histological stains intended by the manufacturer for in vitro diagnostic procedures)• Specimen receptacles
Class B	<p>(Moderate individual and/or low public health risk)</p> <ul style="list-style-type: none">• Clinical chemistry tests• Endocrinology• Allergy• Some specific self-test IVDs• Default class if no other class applies
Class C	<p>(High individual or moderate public health risk)</p> <ul style="list-style-type: none">• Testing for transfusion/transplantation/cell therapy compatibility excluding high-risk blood grouping• Tests for infectious disease, cancer biomarkers• Companion diagnostics/genetic testing/congenital disorders• Monitoring high-risk medicines/substances• Most self-test IVDs
Class D	<p>(High individual and high public health risk)</p> <ul style="list-style-type: none">• Screening for transmissible agents and for high-risk blood grouping for transfusion, transplantation, cell administration, and life-threatening transmissible agents. Screening where possible high risk of propagation, and detection of infectious load where monitoring determines patient management (e.g., Blood groups ABO, Rh, Kidd, Duffy, Kell; HIV1 and 2, HTLV I/II, Hep B and C, Chagas, screening blood for syphilis)

Using General Laboratory Equipment instruments (GLE) in compliance with IVDR

Typically LC-MS kits fall in the scope of the IVDR due to the way in which the intended use / intended purpose is written in the Instructions For Use (IFU) of LC-MS kits where it is specified their use to provide information related to pathological/physiological conditions on human beings.

This is not necessarily the case for LC-MS instruments because they can be used for several other purposes than to provide information related to pathological/physiological conditions on human beings.

Where the IFU/Instruction Manual (IM) of the LC-MS test kit does not specify that the test must be run on a specific/dedicated IVDR compliant LC-MS instrument, then the test may be run on GLE or RUO labelled LC-MS instruments if they fulfill the technical/functional specifications required by the LC-MS kit as specified in the kit's IFU.

The principle is no different to other types of GLE that would be commonly used for in vitro diagnostic tests—such as pipettes, pipette tips, tabletop centrifuges, vortex mixers, liquid handling systems with shakers for 96 well plates, centrifuges for 96 well plates and even DNA sequencers.

What happens when LC-MS test kits are not IVDR compliant?

Where LC-MS test kits are not IVD-CE marked by the manufacturer (thus compliant to either the IVD Directive 98/79/EC or Regulation 2017/746), and are used for IVD purposes by the laboratory, then Art. 5.5 of the IVDR applies and the health institutions must take responsibility for the results generated.

Article 5.5 of the IVDR explains that, with the exception of the relevant general safety and performance requirements set out in Annex I*, the requirements of this Regulation shall not apply to devices manufactured and used only within health institutions established in the Union, provided that all of the following conditions are met:



- 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 therefore.
- 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); and
- i. The health institution reviews experience gained from clinical use of the devices and takes all necessary corrective actions.

* Annex I to the IVDR includes almost 200 General Safety and Performance Requirements governing risk management, performance evaluation/clinical evidence, stability, information on the design and manufacture of the device, and instructions for use, and is fully applicable from 26 May 2022.

Regulatory requirements applicable to European Health Institutions using in-house devices

The first point that must be clarified is that such requirements, which only grant a partial exclusion to full compliance with the IVDR, are applicable only to European Health Institutions.

Laboratories based outside the EEA (Political EU - 27 Member States +Iceland, Liechtenstein, and Norway) offering test services to EU citizens based on samples shipped to their lab are considered manufacturers of IVDs and thus their assay must comply with the IVDD or IVDR without exceptions. They will have to be IVD CE marked.

What follows are the January 2022 amended timelines applicable to European laboratories for implementing Art. 5.5 conditions impacting in-house devices (IHDs):

May 26th, 2022 onward

The following conditions apply:

Labs need to have evidence that their IHD complies to all relevant General Safety and Performance Requirements (GSPR) of Annex I

(a) Labs cannot transfer their IHDs to another legal entity,

May 26th, 2024 onward

The following conditions apply:

- (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;
- (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:
 - The name and address of the manufacturing health institution
 - The details necessary to identify the devices,
 - 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 therefore.
- (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. (Author's Note: this means implementing Post Market Surveillance as per the IVDR requirements.).

May 26th, 2028 onward

The following conditions apply:

- (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.

Complying with Article 5.5

Of all the requirements applicable to in-house devices as of 2022-05-26 the first and perhaps most complex requirement is the one which requires EU laboratories to prove compliance to all Annex I GSPR applicable to their IHD.

This is no light work since the level of evidence required typically represents, as those IVD manufacturers who already prepared for IVDR know well, months of work and several hundred pages of indexed evidence.

Although this requirement is applicable as of May 26th, 2022, starting from May 26th, 2024, laboratories using IHDs will have to officially declare (supposedly in an internal document) compliance with all IVDR applicable GSPRs to their IHD as per Art. 5.5(f). An EU guidance document is in the making for IHD that has a template for such declaration.

Compliance with the other Art. 5.5 requirements - listed in its various sub-points varies in complexity as follows:

- (a) compliance with this requirement is relatively straightforward since very few (if at all) labs do transfer their IHDs to other labs.
- (b) compliance with this requirement is less evident since the request is for the lab to have an adequate QMS for the manufacture and use of such assays. While the use of an IHD by a lab can be adequately covered by the ISO 15189 standard, its manufacturing may require the (albeit partial) implementation of the most specific standard ISO 13485: 2016. At the time of writing this particular point it is still unknown and, perhaps, should be the subject of future guidelines or clarifications.
- (c) & (i) compliance with these requirements is generally already covered in an ISO 15189 compliant laboratory, although the review of experience gained from clinical use (Vigilance & Post Market Surveillance) required by 5.5.(i) is now a regulatory requirement rather than recommended practice.
- (e) this requirement is only applicable upon specific requests from the competent authorities of the country where the laboratory is located.
- (g) is only applicable to devices classified as class D devices while the exact applicability of (h) is still unclear and will need to be subject to further clarification but it remains true that compliance with the applicable Annex I GSPR already implies that the laboratory needs to have adequate technical documentation in support of its IHDs.
- (d) Finally requirement (d) is the one that forces EU health institutions to justify 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. While it is already clear that the concept of "equivalence" centers on the performance of the device (analytical and clinical performance), this is an area which will likely need additional guidance on the exact interpretation of terms like 'equivalent' and 'patient-specific needs'.

On a final note, Art. 5.5. ends with the statements that:



Member States may require that such health institutions submit to the competent authority any further relevant information about such devices which have been manufactured and used on their territory. Member States shall retain the right to restrict the manufacture and use of any specific type of such devices and shall be permitted access to inspect the activities of the health institutions.

This paragraph shall not apply to devices that are manufactured on an industrial scale.

This is important as it implies that a certain level of flexibility has been given to member states to implement further requirements in terms of information/documentation to provide, as well as allowing member states to set specific restrictions . This could thus result in quite divergent approaches to IHDs in the various member states.

The very last sentence of the paragraph adds an additional factor on which the exemption hinges; the concept of the IHDs not being manufactured on an industrial scale. Unfortunately, the term "industrial scale" remains undefined. It has been suggested that industrial scale is not simply defined by the number of devices manufactured, but is also related to commercial aspects. If the manufacturing activity of an IHD is carried out for commercial purposes, it should be considered as production on an industrial scale. The spirit behind the exemption provisions in Art. 5.5. is that this should only be applicable to devices that are produced by the health institutions in order to meet a patient groups' specific needs, and therefore, the manufacturing process should not produce more than the estimated number of required devices. Thus, industrial scale is not synonymous to "mass-production" nor is the analysis of a large number of patients automatically meaning the production is on industrial scale.

Conclusion

The IVDR is surely set to transform the landscape for in vitro diagnostics in the EU, ultimately benefiting patients through safer and improved commercial and in-house developed diagnostic tests. However, the impact of the IVDR on clinical laboratories is highly significant. A survey of 150 laboratories found on average that they had implemented 52% IVD CE-marked IVDs, 14% modified or off-label CE-IVDs, 8% RUO, and 26% IHDs.¹² These in-house developed devices that make up almost a quarter of their portfolio are crucial for patient diagnosis and monitoring in a wide range of rare and/or emerging diseases across almost all fields of medicine.

For IVD developers, manufacturers, and end-users, some uncertainty and grey areas remain with respect to interpreting the new Regulation and how it affects different reagents, components, products, processes, and instruments. This is especially the case for clinical laboratories that often integrate test kits and instrumentation from different vendors to create bespoke devices to meet specific patient needs. However, analysis of the IVDR reveals areas of flexibility. Many IVD CE-marked assays/kits do not specify on which LC-MS instrument their kit has to be used. Where the IFU/IM of the LC-MS test kit does not specify the use of an IVD-CE marked LC-MS instrument (either compliant to the IVDD or IVDR), the test may be run on general laboratory use (GLE) LC-MS instruments because, by IVD CE marking its kit, the LC-MS test kit manufacturer takes full responsibility that the results obtained by that combination fully meet all of the applicable GSPR requirements of the IVDR.

Where LC-MS test kits are not IVD-CE marked (thus in compliance either with the IVDD or IVDR), then the resulting assay falls in the in-house device category and the health institution must take responsibility for its compliance to all applicable IVDR Annex I General Safety and Performance requirements as above explained.

Although this is already applicable since May 26th, 2022, the enforcement hasn't started abruptly, and, based on our observations, labs have some flexibility to prepare.

However, it has to be clear that the enforcement of Art. 5.5 requirements exclusively pertains to the Competent Health Authorities of the EU Member State where the lab is located. Therefore, it may be possible that the enforcement actions will not have the same speed across the 27 European Member States.

The reason why clause 5.5(d), which will prohibit any EU lab to do its own IHD if there is an equivalent (industry IVD-CE marked) assay on the market, has been postponed till May 26th, 2028, is that by then all IVD assays on the market will have to be compliant to the IVDR. That will allow laboratories to verify and document whether or not "equivalent" assays (IVDR CE-marked) are available on the market. In the meantime, collaborative efforts are underway by professional societies and device manufacturers to obtain or establish clear interpretations of terms such as 'equivalence' and 'patient needs', which will be essential to put in place before these conditions can be met.

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