MEDTECH & PHARMA
PLATFORM

Position Paper

Impact of the IVDR on the use of in-house devices by health institutions and central laboratories in clinical trials

October 2024

Executive summary

In this position paper, the MPP Association explores challenges linked to the use of in-house devices by health institutions and central laboratories in clinical trials and proposes solutions to strengthen the pipeline for in-house *in-vitro* diagnostic medical devices (IVDs).

In particular, the MPP Association proposes the following leads to address those challenges:

- Clarification of the scope of the health institution's definition, extending its scope to central laboratories;
- Provision of a clear definition of health institution with the next revision of the IVDR, expected in 2027;
- Provision of an additional transitional period to health institutions to enable them to carry out the initial research for equivalent devices for all their in-house devices according to Article 5(5)(d) of the *In Vitro* Diagnostics Regulation (IVDR);
- More guidance and training to clarify the IVDR's requirements by the European Commission, European Medicines Agency (EMA) and National Competent Authorities would support the building of a better understanding of the scope. In addition, an open dialogue about ambiguities and concerns of health institutions would allow for future alignment.

1. Introduction

The timely availability of medical technologies is critical for patient care and the efficiency of healthcare systems. As vital stakeholders in the clinical trial ecosystem, hospital laboratories, public health institutes and central laboratories play a pivotal role in analyzing an array of patient samples to advance patient care and innovation.

While entities that are called out under the "health institutions" definition (e.g., hospitals) support clinical trial testing in the European Union (EU), most clinical trial sponsors rely on central laboratories to provide consistent and reliable testing for the same clinical trial conducted across multiple jurisdictions. Specifically, central laboratories provide standardized, high-quality testing services across various trials, performing a wide range of tests necessary to conduct clinical trials.

To extract diagnoses or pertinent diagnostic insights from these samples, hospital laboratories, public health institutes, and central laboratories rely on two main categories of tests:

- CE-marked IVDs are labelled with the "Conformité Européenne" (CE) mark required to distribute and sell them on the EU market. Despite being commercially available, CE-marked IVDs are used to a limited extent due to the unavailability of products necessary to perform the necessary tests.

Medtech & Pharma Platform Association
www.medtech-pharma.com | association@medtech-pharma.com

- In-house IVDs are developed on a non-industrial scale to address the specific needs of target patient groups that cannot be met at the appropriate level of performance by an equivalent CE-marked device available on the market. As such, in-house IVDs constitute the lion's share of IVDs used by hospital laboratories, public health institutes and central laboratories during clinical trials.

In-house IVDs are essential for patient care and for conducting clinical trials, which involve rigorous testing of new drugs, medical devices, or treatments to assess their safety and efficacy. Using in-house IVDs in clinical trials allows researchers to develop and implement necessary assays agilely and quickly for the targeted use. Such assays are used to test blood chemistry, hematology, and genetic analyses.

When used in a health institution established in the EU, the following IVDs are deemed in-house IVDs:

- Non-CE-marked IVDs, manufactured within the same health institution on a non-industrial scale;
- CE-marked IVDs that are modified or used outside of the instructions for use and used within this same health institution;
- Commercial Research Use Only (RUO) where a health institution ascribes to them an intended purpose such that they would meet the definition in Article 2(2) of Regulation (EU) 2017/746 on In Vitro Diagnostics (IVDR).

Given the essential role that in-house IVDs play in patient care and clinical trials, the MPP Association[1] is of the opinion that it is important that the scope and regulatory framework for their use are clarified to facilitate innovation and ultimately improve patient care outcomes.

2. Impacts of the IVDR on in-house IVDs and clinical trials in the EU

In-house IVDs developed by health institutions[2] are exempt from most of the provisions of the IVDR[3], provided that the health institution adheres to the conditions laid out in Article 5(5) of the IVDR[4]. Nonetheless, the interpretation and implementation of the IVDR's health institution requirements pose significant challenges to the utilization of in-house IVDs in the EU. In this position paper, we explore these challenges and propose solutions to strengthen the pipeline for in-house IVDs, thereby ensuring the well-being of patients and enhancing healthcare systems' effectiveness across Europe.

First, it is unclear whether central laboratories are covered by the health institution definition, as set out in Article 2(29) of the IVDR. This ambiguity creates an uneven playing field and poses significant legal uncertainty for sponsors of clinical trials as well as central laboratories performing tests of patient samples in the context of clinical trials. As set out above, the European clinical trials ecosystem predominantly relies on central laboratories to support related diagnostic tests.

Currently, some central laboratories take the view that they meet the 'health institution' definition, while others are awaiting clearer legal guidelines.

[1] Please note that the positions are endorsed by and represent the aligned view of members of MPP, which have commonly decided to communicate their position through MPP. The position paper has been subject of abstentions by Roche Holding and does not represent the company's position.

[2] As defined by the IVDR, health institutions encompass public and private organizations primarily dedicated to patient care, treatment, and public health initiatives.

[3] R*egulation (EU) 2017/746 of the European Parliament and of the Council of 5 April 2017 on in vitro diagnostic medical devices and repealing Directive 98/79/EC and Commission Decision 2010/227/EU.*
OJ L 117, 5.5.2017, p. 176–332. http://data.europa.eu/eli/reg/2017/746/oj

[4] It is important to note that national legislation could impose supplementary regulations, necessitating consultation with national competent authorities to ensure compliance with performance study mandates and pertinent regulatory standards, which may affect in particular the national definition of a "health institution", though the supplementary legislative power of the member states is not limited to this aspect. Albeit outside the scope of this position paper, clarification and streamlining of these regulatory ambiguities are imperative to foster innovation, expedite healthcare advancements, and ultimately enhance patient outcomes.

Without access to central laboratories in the EU, clinical trials are likely to be delayed or conducted in other jurisdictions that provide more legal certainty – a trend that is already visible.

Second, the conditions applicable to health institutions are currently unclear, leading to significant legal uncertainty for clinical trial sponsors. In particular, clinical trial sponsors are concerned about claims of data integrity issues relating to laboratories used to analyze data from their clinical trials. Due to limited clarity and guidance of current rules, hospital laboratories, public health institutes, and central laboratories have adopted their own interpretations and approaches, leaving it to clinical trial sponsors to assess the risks.

According to a survey conducted by the Association For Molecular Pathology (AMP) in 2024[5], hospital laboratories, public health institutes, and central laboratories reported major challenges to their laboratory and testing practices following the entry into force of the IVDR due to:

- Lack of harmonized implementation and increased confusion within the laboratory
- diagnostics community;
- Increase in costs due to the implementation of new practices and models;
- Lack of resources to support the implementation of changes;
- Lack of guidance;
- Lack of communication by institutions;
- Limited ability for health institutions (hospitals, clinics, and laboratories) to develop their own IVDs.

Due to these challenges, clinical trials sponsors have started exploring other jurisdictions to conduct clinical trials and the possibility of discontinuing certain in-house devices in the EU; distribution of in-house-developed reagents to other laboratories has been stopped since this is not allowed under the IVDR if the “in-house” status is to be maintained.

In this context, the MPP Association would like to highlight the urgent need for clarifications regarding the scope of the health institution definition and its conditions.

a. Clarification needed on the scope of the health institution definition

It is currently unclear whether the definition of health institution covers central laboratories. A clear definition categorizing central laboratories as health institutions under the IVDR is currently missing and it poses significant challenges for the tests developed and conducted in these facilities for the purposes of clinical trials. Today, the general conservative view is that central laboratories do not fall within the scope of the health institution definition and thus cannot benefit from the exemptions by complying with the relevant requirements for the use of in-house IVDs in the same manner as hospital laboratories and public health institutes.

For background purposes, it should be noted that the current regulatory framework, particularly the IVDR and Medical Device Coordination Group (MDCG)[6] guidelines do not help resolve the uncertainty regarding the inclusion of central laboratories within the definition of 'health institution'. The IVDR delineates specific restrictions on the use of in-house IVDs, confining them to designated 'health institutions' defined as organizations primarily dedicated to patient care, treatment, or public health promotion. With the health institution exemption, the IVDR acknowledges the need - for in-house devices - for derogations from the rigorous conformity assessment procedures required for commercial devices; however, it fails to provide clarity on whether central laboratories are eligible for

[5] AMP. *The Impacts of the European Union In Vitro Diagnostic: Regulation Survey*. February 2024. Last accessed on 23 September 2024. https://www.amp.org/AMP/assets/File/advocacy/Impacts_of_the_EU_IVDR_Survey_Report_FINAL.pdf?pass=18.

[6] Medical Device Coordination Group Working Groups. Last accessed on 23 September 2024. https://health.ec.europa.eu/medical-devices-dialogue-between-interested-parties/medical-device-coordination-group-working-groups_en

such derogations, especially considering the shortage of CE-marked assays for specialized needs such as in the case of clinical trials.

Today, the interpretation and application of the health institution concept have created an uneven playing field among central laboratories, which does not align with the spirit of the IVDR. This has sparked contention and ambiguity, hindering the seamless integration of in-house IVDs into clinical practices. Ultimately, European patients are those that are at risk if clinical trials are delayed or occur outside of Europe due to the challenges posed by current regulations.

As Europe endeavors to accelerate clinical trials through initiatives like *Accelerating Clinical Trials in the EU* (ACT EU)[7], the unresolved issues surrounding the regulatory framework for in-house devices present a threat to this ambitious goal.

Without decisive action to address the challenges and clarify the scope of the 'health institution' definition – including its establishment requirements – the intended benefits of in-house IVDs will remain unrealized. More importantly, the lack of access for clinical trial sponsors to central laboratories capable of handling large-scale testing of patient samples has already started to undermine patient well-being and poses significant challenges in data integrity concerning standardized data collection and impede the effectiveness of healthcare systems across Europe.

b. Guidance needed on key items for health institution exemption

Health institutions wishing to benefit from the exemption set out in Article 5(5) are subject to rigorous requirements. However, several key provisions set out in Article 5(5) are unclear, and further guidance is necessary to ensure the correct and harmonized application of the rules.

In particular, three key items need clarification:

1) In relation to Article 5(5)(d), what do 'equivalent' and 'patient-specific needs' mean?
2) What rules apply to the different categories of in-house devices?
3) What does the establishment requirement mean for Mutual Recognition Agreements (MRA) between the EU and third countries?

(1) In relation to Article 5(5)(d), what do* 'equivalent' and 'patient-specific needs' *mean?

A requirement for health institutions to be able to develop in-house IVDs is that they can only be used if there is no "*equivalent*" CE-marked IVD on the market, or when a target "*patient group's specific needs*" cannot be met at the appropriate level of performance by an equivalent CE-marked IVD.

Appropriate interpretation of clauses and the definition of these terms is crucial, as they are the basis that should enable laboratories to compose an optimal portfolio of CE-marked IVDs and in-house IVDs.

(2) What rules apply to the different categories of in-house devices?

The definition of an in-house IVD, and the gray areas between in-house IVDs as interpreted historically, CE-marked IVDs, the use of modified CE-marked IVDs, and the use of Research Use Only (RUO) tests must be clarified. The challenge lies in defining the boundaries between different types of IVDs – specifically, what rules apply to and who is responsible (clinical trial sponsors or laboratories) for the different types of IVDs:

- **CE-marked IVDs**: Commercially available IVDs with a CE mark used within the intended purpose;
- **Modified CE-marked IVDs**: Commercially available IVDs with a CE mark modified by laboratories, for specific purposes outside the intended use;
- **RUO Tests**: Tests intended for research only and not for clinical diagnosis;

[7] Accelerating Clinical Trials in the EU (ACT EU). Last accessed on 23 September 2024. https://www.ema.europa.eu/en/human-regulatory-overview/research-development/clinical-trials-human-medicines/accelerating-clinical-trials-eu-act-eu

- **In-house IVDs**: IVDs developed and used within a laboratory.

(3) What does the establishment requirement mean for Mutual Recognition Agreements (MRA) between the EU and third countries?

Additionally, the requirement that health institutions must be established within the European Union (EU) poses challenges if impacted institutions serving EU-based clinical research are located outside the EU.

Today, the IVDR implies that health institutions not established in the EU but offering diagnostic or therapeutic services to a natural or legal person established in the EU cannot use in-house devices in that context. They are required to make available a copy of the EU declaration of conformity of the CE-marked devices used, upon request by an EU competent authority. Compliance with this requirement is posing a challenge in the context of EU efforts to attract clinical trials sponsors and facilitate clinical trials. Data must be available in Europe in order to support marketing approvals of innovative therapies; the requirements applicable to health institutions outside of the EU constitute a hurdle in this context.

It is important that health institutions outside of the EU are considered eligible if they fulfill the other requirements, and with an MRA between a third country and the EU in place, they should be able to function under the IVDR's health institution definition.

3. Proposed solutions for regulatory clarity for in-house device approval

In response to the challenges outlined above, we present the following proposed solutions aiming to mitigate the identified issues and enhance regulatory clarity within the context of in-house device approval.

a. Clarification of the health institution definition

A revision of MDCG 2022-10[8], currently in progress, should aim to create common terminology and requirements for the 'health institution' exemption. As part of this revision, the MPP Association proposes to add an explicit statement to assert that central laboratories, including those not part of public institutions, fall within the scope of the IVDR's health institutions definition. This clarification would align stakeholders' interpretations and ensure consistent application of the regulations across the EU. It would be beneficial if, in the revision of MDCG 2022-10, a statement could be added to assert that where an MRA is in place between the EU and third countries, covering relevant regulatory and oversight aspects of IVDs, health institutions established in the third country would fall within the scope of the IVDR's health institutions definition.

Moreover, as part of the revision of MDCG 2022-10, it would be helpful to provide guidance on the implications of the boundaries between different types of IVDs and their uses within health institutions. Greater clarification on the responsibilities of different actors when using such types of IVDs would also be welcomed.

Finally, the MPP Association also proposes to revise MDCG 2023-1 on the health institution exception under Article 5(5) of the MDR and IVDR to clarify the health institution definition.

b. EUDAMED roll-out

A European database on medical devices (EUDAMED) is crucial for implementing the IVDR's requirements and ensuring compliance with the Regulation. Once fully functional, the EUDAMED

[8] MDCG. *MDCG 2022-10 Q&A on the interface between Regulation (EU) 536/2014 on clinical trials for medicinal products for human use (CTR) and Regulation (EU) 2017/746 on in vitro diagnostic medical devices (IVDR)*. Last accessed on 23 September 2024. https://health.ec.europa.eu/system/files/2022-05/mdcg_2022-10_en.pdf

database is expected to be the major source of information about equivalent devices available on the market. This information is expected to be relevant for health institutions to show compliance with Article 5(5)(d) of the IVDR, according to which there must be no "*equivalent device available on the market*" for an IVD to qualify as in-house device.

The deadline for manufacturers to CE mark class C devices under the IVDR is May 2026 and Article 5(5)(d) will apply from May 2030 onwards. To be able to meet the "*equivalent*" requirement, the MPP Association proposes to provide a transition period to health institutions to carry out the initial search for equivalent devices for all their in-house devices.

c. Additional education and communications to assist with streamlining the regulatory process.

More guidance and training to clarify the IVDR's requirements by the European Commission, European Medicines Agency (EMA) and National Competent Authorities would support the building of a better understanding of the scope. In addition, an open dialogue about ambiguities and concerns of health institutions would allow for future alignment. Such guidelines might consider the practical challenges for clinical trial sponsors and health institutions, including hospital laboratories, public health institutes, and central laboratories.

New or updated guidance should explicitly address other laboratories providing essential services for patient management within the definition of health institutions, especially in the context of clinical trials. Although this approach may take time, it would provide legal certainty and resolve diverging interpretations among industry stakeholders, Notified Bodies, and National Competent Authorities.

d. Amending the IVDR

The MPP Association would welcome a clear definition of health institution as part of the next revision of the IVDR, expected in 2027. This legislative mechanism would provide a binding clarification, albeit not expedient, ensuring legal certainty for the future. As part of this revision, legislators should consider explicitly including central laboratories, whether public or private, whose primary purpose is patient management or public health promotion under Article 2(29) of the IVDR (i.e., the definition of health institution).

4. Conclusion

Addressing the challenges faced by in-house IVDs in meeting the IVDR requirements is crucial for ensuring timely access to medical technologies, conducting clinical trials, and advancing healthcare in Europe. There is a clinical need for both CE-marked IVDs and in-house IVDs, as there is for modified CE-marked IVDs, and RUO tests.

By clarifying the scope and the regulatory framework of the use of in-house IVDs by hospital laboratories, public health institutes, and central laboratories through revisions of existing guidelines or legislative amendments, we can strengthen and facilitate innovation and ultimately improve patient care outcomes. It is imperative that stakeholders collaborate to implement these solutions and navigate the regulatory landscape effectively, ensuring the continued progress of healthcare delivery in Europe and the optimization of patient care.

The MPP Association urges all involved stakeholders (European Commission, European Medicines Agency, and National Competent Authorities) to engage in discussions with clinical trial sponsors, the clinical laboratory community, and regulatory experts to ensure that laboratories can meet the IVDR

standards. Recognizing central laboratories as health institutions with regard to laboratory testing would facilitate and enhance their role in patient care, streamline regulatory processes, and foster collaboration within the healthcare system. Addressing these challenges effectively is crucial to ensure patient care remains uncompromised during the transition to the new IVDR standards. Regulatory bodies, laboratories, and healthcare providers must collaborate to mitigate these implications and prioritize patient well-being.

About the Medtech & Pharma Platform Association

The Medtech & Pharma Platform Association (MPP) brings together companies from the pharmaceutical, medtech, diagnostic and tech sectors and provides opportunities to exchange knowledge and to collaborate in technology and regulatory areas related to combined products.

The MPP's objectives are:

- To enhance synergies between the pharma, medtech, diagnostic and tech industries,
- To establish new collaboration models to ensure and accelerate market access for safe and innovative treatment options,
- To work toward the development of a balanced and proportionate regulatory and policy framework for combined products including connected combined products.