Questions and Answers on In-house Devices under Article 5.5 of the Regulation (EU) 2017/746 on In-vitro Diagnostic Medical Devices (IVDR)

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Table of Contents

1 Purpose and Applicability

1.1 Purpose

This Questions & Answers document is intended to support understanding of provisions stipulated in Article 5.5 of the European Regulation (EU) 2017/746 on in vitro diagnostic medical devices (IVDR) [1] regarding the development, manufacturing, and use of in vitro diagnostic medical devices (IVD) within a health institution (e.g., medical laboratory) for specific patients' needs.

The content of this document is based on guidelines provided by the Medical Device Coordination Group (MDCG) in "MDCG 2023-1 Guidance on the health institution exemption under Article 5.5 of Regulation (EU) 2017/745 and Regulation (EU) 2017/746" [5]. However, there can be more-specific national provisions in the EU member states regarding Art. 5.5 IVDR in place that shall be considered by the health institutions.

In the IVDR, there is no specific term or definition provided pertaining to Article 5.5. Therefore, several terms are used in the context of Art. 5.5 IVDR:

- In-house Test/Assay/Device
- Lab-developed Test/Assay/Device
- Home-brewed Test/Assay/Device, or
- User-defined Method.

Since the MDCG Guidance 2023-1 [5] refers to "in-house device" (IHD), this term will be used in this document.

1.2 Applicability

This document can be used within Siemens Healthineers to foster understanding of the provisions stipulated in Art. 5.5 IVDR and MDCG Guidance MDCG 2023-1 [5] pertaining to health institutions manufacturing or modifying and using IVD products in-house.

2 Disclaimer

Information provided in this document was compiled diligently to the best of our ability and conscience to ensure that the interpretations provided are sound.

Despite the utmost care, we cannot assume any guarantee that the information is correct, and we don't accept any legal responsibility for it.

The interpretations provided in this document are for information purposes only. Any consideration of the information is the reader's own responsibility and is not meant to substitute for specific legal advice.

Please consider that the ultimate interpretation of legal requirements lies with the courts.

This document may be changed or amended at any time without notice to ensure that the information is kept up to date.

3 General information and terms relevant under Article 5.5 IVDR

3.1 What is considered an IHD?

Short answer

There is no official definition of an IHD in the IVDR, but the related MDCG Guidance provides a high-level definition of IHD [5].

In-house device: a device that is manufactured and used only within a health institution established in the EU and that meets all conditions set in Article 5.5 of the IVDR and is used within that same health institution.

Explanatory information

The MDCG Guidance provides the following definition of IHD [5]:

In-house device: a device that is manufactured and used only within a health institution established in the EU and that meets all conditions set in Article 5.5 of the IVDR and is used within that same health institution.

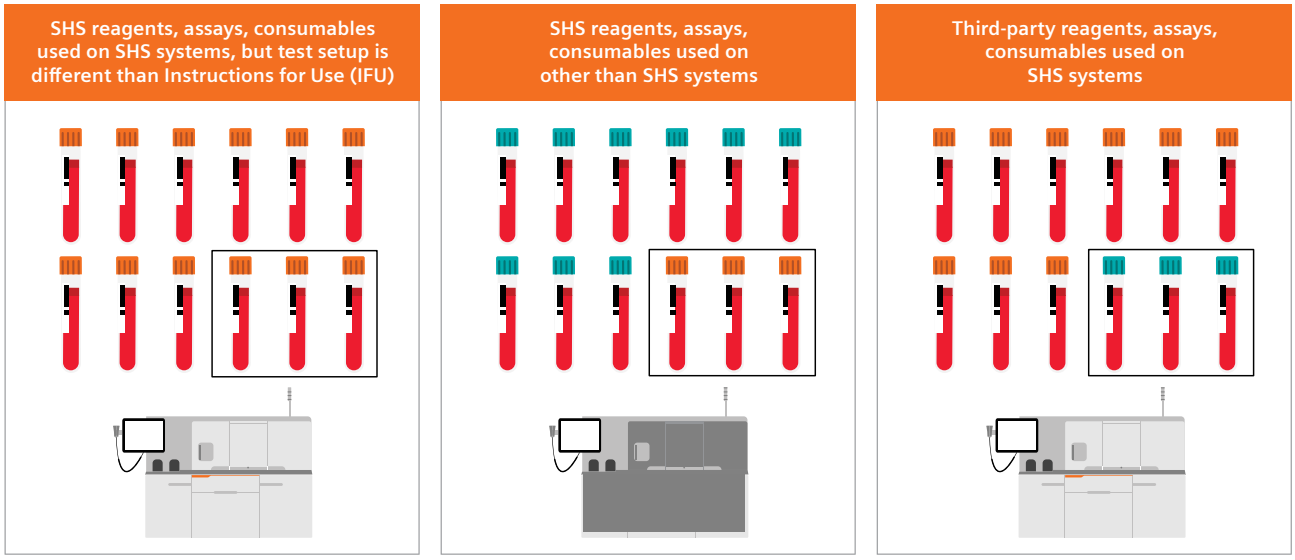
Examples of IHD:

- PCR master mix: a health institution orders primers based on scientific literature and manufactures its own in-house master mix containing buffer, primers, dNTPs, cofactors, and enzymes to run PCRs on human DNA/RNA samples.
- A health institution develops in-house a medical software that is used on-site by its medical staff.

Important: IHDs were entirely exempted from the IVDD. The situation changed under the IVDR, and health institutions performing the following activities could unintentionally fall within the scope of Art. 5.5 IVDR, if one of the following criteria is met:

- CE-marked IVD is used for a purpose not intended by the manufacturer.
- CE-marked IVD is modified for a new purpose or patient target group not covered by the manufacturer's IFU.
- Significant deviations are made from manufacturer's instructions for use that alter the function, performance, or intended purpose of a CE-marked IVD.
- Sample types, accessories, or components or combining devices not specified by the manufacturer are used.
- A device is used outside of the manufacturer's instructions (called "off-label use").
- A User-defined Method is developed and used that significantly modifies a CE-marked IVD and validated combination of devices.
- RUO products are used for diagnosis or other clinical decision purposes.

In Annex 2 (see section 8) and Annex 3 (see section 9), you can find two flowcharts that may be helpful in assessing if an activity or modification planned by the health institution could fall under Art. 5.5 IVDR.



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3.2 What has changed for In-house devices (IHD) under IVDR?

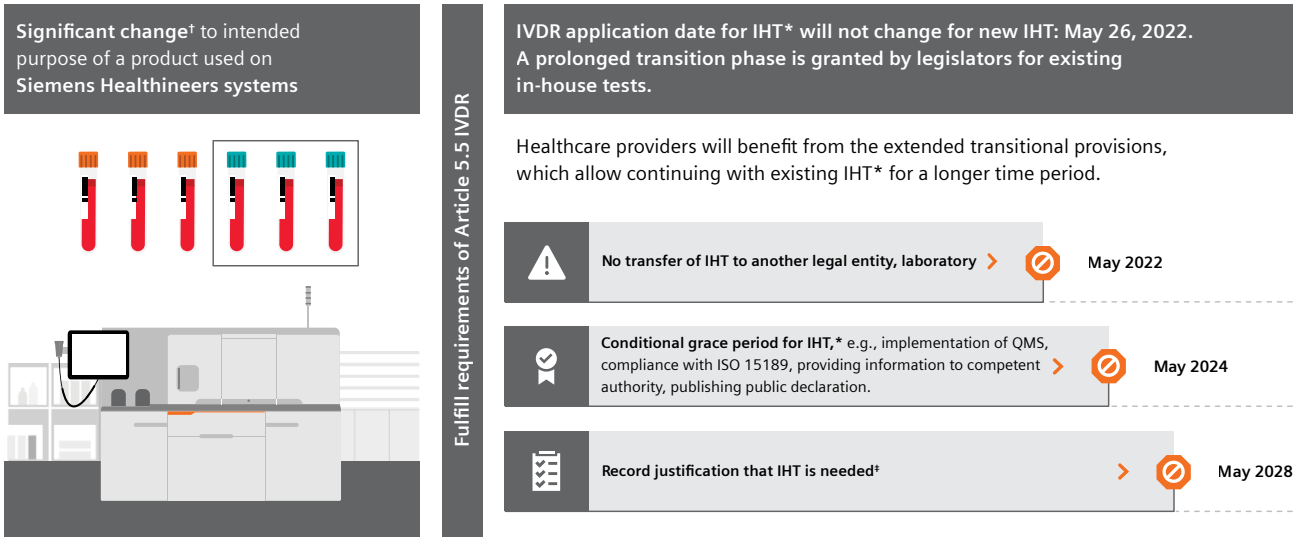
Short answer

Under the predecessor European legislation, the Directive (EC) 98/79/EEC on in vitro diagnostic medical devices (IVDD) [2], an IVD that is manufactured and used within the same health institution is excluded entirely from the requirements of this directive and is regulated only under national laws of the EU member states.

Explanatory information

In contrast to the IVDD, the IVDR introduced dedicated provisions pertaining to IHD that must be applied, and health institutions and IHD are subject to expanded requirements, which are defined in IVDR Article 5. Section 5. For relevant legal references, refer to Section 9 of the document or directly to the IVDR. [1].

The IVDR is formally applicable from 26 May 2022, but for most requirements stipulated in Art. 5.5, a prolonged transition time is granted. See the image below and question 4.10 for detailed timelines.



*Lab operations can include in-house tests (IHT), lab-developed tests (LDT), research use only (RUO), user-defined methods (UDM), and off-label use of a CE-marked IVD.
†Significant change may include but is not limited to design change, change of intended purpose, specimen type change, adding indications for use, changing/adding testing population. Example: modification of a CE-marked device.
‡Record justification that IHT is needed: Proof of other specific needs of targeted patients that cannot be met at the appropriate level of performance by the equivalent CE-marked device available on the market.

The Medical Devices Coordination Group (MDCG) developed European guidance on IHD [5] and the application of Article 5.5 IVDR by health institutions. However, certain areas covered by Article 5.5 EU MDR/IVDR may be subject to national approaches or enforcement interpretation, e.g., the definition of a "legal entity," the interpretation of what is an "equivalent device" remains broad, the understanding of what is "manufactured at an industrial scale" remains very broad and flexible.

Thus, some EU member states may implement national rules or guidance documents for IHD that must be followed by the health institutions based in those countries in addition to the general EU-wide provisions.

Furthermore, according to the second paragraph of Article 5.5, EU member states may restrict the manufacture and use of any specific type of IHD. Health institutions are advised to contact their competent authority or consult national legislations for possible restrictions in their EU country.

3.3 Why are IHDs still needed?

Short answer
IHDs are needed to address special needs of patients that remain unmet by CE-marked IVDs and can also be used to foster innovation in in vitro diagnostics.

Explanatory information
Commercial tests developed by manufacturers may not be available for all diagnostically relevant parameters. In such situations, IHDs allow for diagnosis and management of certain tests, e.g., assays for rare diseases, screening in niche areas such as organs for transplantation, tests associated with high costs and low reimbursement, tests based on new technologies and technologies that cannot be conserved in the box (e.g., cell culture), and fast response in outbreak situations such as for SARS-CoV-2.

Some IHDs are based on single components (e.g., monoclonal antibodies) that may be used as building blocks to assemble a panel for specific diagnostic purposes.

Patient care can benefit from faster implementation of innovative technologies through initial use of IHDs. Most recently, NGS and digital PCR represented such improvements. In the long term, such new technologies might become standard for IVDs that are CE-marked as well. Without IHDs, the innovation cycles would be much longer and could delay useful tools for improved patient care.

3.4 What are the provisions for IHDs under IVDR?

Short answer
Health institutions manufacturing and using IHDs benefit from an exemption and must fulfill only the requirements stipulated in Art. 5.5 and not the entire IVDR.

Explanatory information
An exemption exists for health institutions that manufacture, modify, and use IVDs in-house to address unmet patient needs. This exemption sets out that these IHDs need not meet the entire IVDR but only selected requirements that are defined in Article 5.5 of the IVDR.

In general, health institutions falling under Article 5.5 exemption must meet the relevant requirements of IVDR Annex I (General Safety and Performance Requirements, GSPR), operate under an appropriate quality management system, justify using the in-house exemption, and fulfill certain documentation, registration, and post-market surveillance requirements. The MDCG document 2023-1 [5] provides guidelines on the application of some of these rules by healthcare professionals aiming to design, manufacture, modify, and use IHD. In addition, this guidance document intends to foster harmonized application of Article 5.5 by the national competent authorities responsible for its enforcement.

If the health institution does not meet all the requirements set out in Article 5.5 when manufacturing or using a device, the device that is manufactured and used by the health institution must comply with all the requirements of the IVD Regulation, including the CE-marking process.

3.5 What is NOT considered an IHD?

Short answer
- Devices that are not manufactured, modified, or used within one health institution
- Devices for self-testing used outside of the health institution
- Manufacturing of a device purely for economic reasons [5]

Explanatory information
Examples of devices that don't qualify as IHD and cannot benefit from the exemption in Art. 5.5 IVDR:
  - Medical device applications where patients can enter medical data outside the health institution.
  - Self-tests cannot fall under Article 5.5 if used outside the health institution's premises. However, an in-house manufactured self-test can be used within the health institution by lay users. Also, an in-house device can be used in the health institution's laboratory for the analysis of samples collected by patients themselves outside the health institution and consecutively sent to the laboratory.
  - Manufacturing a device purely for economic reasons/financial interests without specific patient needs.

In Annex 2 (see section 8) and Annex 3 (see section 9), you can find two flowcharts that may be helpful in assessing if an activity or modification planned by the health institution could fall under Art. 5.5 IVDR.

3.6 What does the term "device" mean in the context of the IVDR?

Short answer
In vitro diagnostic medical device or an accessory for an IVD.

Explanatory information
The term "device" mentioned in Article 5.5 means an "IVD" as it is defined in Article 2.2 IVDR or "accessory for an IVD" as defined in Article 2.4 of the IVDR.

Note: A protocol in the form of a written procedure that is shared between health institutions, patient specimens, and results are not considered to be devices according to the definitions above. Consequently, the IVDR doesn't apply to them.

3.7 What is understood by the term "health institution?"

Short answer
Health institution means an organization established in the EU with the primary purpose of care or treatment of patients or the promotion of public health. It could be e.g., a hospital, university, medical or private laboratory, doctor's office, pharmaceutical labs, or public health institute. Organizations providing services related to well-being or a healthy lifestyle are not covered by this definition.

An individual healthcare professional (e.g., a physician) is not considered a health institution and is not in scope of Article 5.5.

Explanatory information
Article 2.29 of the IVDR provides the following definition:

"'Health institution' means an organization the primary purpose of which is the care or treatment of patients or the promotion of public health;"

For a health institution to fall under the exemption set out in Art. 5.5 IVDR, it must be established in the European Union.

The definition of health institutions includes hospitals as well as institutions, such as laboratories and public health institutes, that support the healthcare system and/or address patient needs, even if they do not treat or care for patients directly.

In contrast, organizations promoting healthy lifestyles or well-being, such as gyms, spas, and wellness and fitness centers are not considered health institutions.

Recognition as a health institution can also depend on national legislation and could therefore differ among EU Member States. However, individual healthcare professionals (e.g., physicians) do not fall under the definition of "health institution," and Article 5.5 doesn't apply to their activities.

3.8 May health institutions be based outside the EU and benefit from the exemption of Art. 5.5?

Short answer
No.

Explanatory information
The exemption from Article 5.5 IVDR is applicable to health institutions within the EU only. According to IVDR Article 6.2 on distance sales, health institutions outside the Union that offer diagnostic or therapeutic services through distance sales to patients in the EU must use devices that comply with the IVDR, without having the possibility of applying the in-house exemption. [5]

3.9 What is meant by "manufactured and used within the same health institution" in the context of Art. 5.5?

Short answer
Manufacturing covers activities undertaken by a health institution to produce a new IVD, combine devices to a new IVD, or significantly modify an existing IVD product.

The IHD can be used within one healthcare provider, such as a university with several labs, or a private lab chain with several labs in the EU.

Use within the same health institution implies that the product cannot be transferred to another organization or person, e.g., another health institution or any other natural or legal person. However, the concept of "legal entity" can differ, and national competent authorities may define this aspect in national legislation.

If the IVD product will be used outside the health institution's legal entity, e.g., a self-test used by a patient at home, it cannot be considered IHD.

IVD products manufactured in-house purely for economic interests cannot be considered IHD.

Explanatory information
The exemption under Art 5.5 applies to devices that are manufactured and used within health institutions, except for devices for performance studies.

"Manufacturing" implies activity undertaken by the health institution to produce an IVD. This can include:

- Assembling an assay from raw materials and components,
- Making a new device from CE-marked IVDs,
- Changing the intended purpose of a CE-marked IVD product,
- Combining IVD devices into a new product,
- Modifying an existing IVD device to create a new product, or
- Assigning a medical purpose to a device that is not an IVD (e.g., research use only instrument or reagents) for the purpose of providing diagnostic or patient management information.

A significant change or modification of an IVD product or its intended purpose is a modification made by a health institution that was not intended by the manufacturer and has an impact on the conformity of the product with the IVDR. Neither the IVDR nor the MDCG Guidance 2023-1 [5] define what can be considered as significant change or modification of an IVD device, but the following guidelines (see [6]) may be helpful for this verification.

If the health institution manufactures IVD products in-house purely for economic or financial interests and without clinical reasons, Article 5.5 cannot be applied.

The health institution may use the CE-marked IVD in translational research without triggering obligations under Art. 5.5 if this research does not provide any diagnostic or patient management information: Such use falls outside the scope of the IVDR (concept of research use only [RUO]).

The "use" of a device should take place within the same health institution in the EU, which implies that the device cannot be transferred to another health institution or indeed to any other natural or legal person. According to IVDR preamble 28, that use should be understood to include measurement and delivery of results.

This use within health institutions can either be physically or, e.g., for medical device software, remotely, provided the device is not made available to another legal entity. The act of using an in-house manufactured device is performed within the health institution when the device is used in the care or diagnosis of a patient. If the device is used outside the health institution's premises, it cannot be considered as IHD, e.g., an IHD for self-testing that would be used by the patient at home. However, an in-house manufactured self-test can be used within the health institution by laypersons. An in-house device can be used in the health institution's laboratory for the analysis of a specimen that is collected by patients themselves and sent to the laboratory for examination.

Since healthcare systems are organized differently in different EU member states, the definition of the term "legal entity" may differ, e.g., one medical lab can be one legal entity or accommodate several legal entities, or several medical labs can belong to the same legal entity. Thus, the national competent authorities may clarify how the concept of "legal entity" shall be understood nationally.

3.10 What does "manufacturing on an industrial scale" mean in the context of Art. 5.5?

Short answer
IVD products manufactured in-house on an industrial scale may not benefit from the exemption of Article 5.5. "Manufacturing on an industrial scale" is not defined in the IVDR. Thus, the health institution must determine case-by-case, considering different aspects such as e.g., patient needs, volume of production, commercial aspects, and manufacturing process, whether its activities are on an industrial scale or not. It means that e.g., the analysis of a large number of patient specimens does not automatically mean that the IHD is manufactured on an industrial scale.

Explanatory information
If the health institution manufactures the device on an industrial scale, it cannot benefit from the exemption set out in Article 5.5.

There is neither a definition nor clear criteria for industrial-scale manufacturing in the IVDR. The MDCG guidance clarifies that, considering that IHDs are produced by the health institution in order to meet specific needs of a patient group, the manufacturing process should not produce more than the estimated number of required devices. Thus, the analysis of a large number of patient specimens does not automatically equate an in-house IVD to a device produced on an industrial scale.

It may be helpful to consider the interpretation in IMDRF Guidelines Definitions for Personalized Medical Devices [3]: A mass-produced medical device is defined by being "typically produced in a continuous production run or homogenous batch."

However, the term "industrial scale" is not simply defined by the number of devices manufactured; commercial aspects of production should also be considered. Thus, "industrial scale" cannot be considered synonymous to the term "mass-produced," e.g., the analysis of a large number of patient samples does not automatically equate an IHD to a device produced on an industrial scale. On the contrary, if manufacturing of even a smaller number of IHDs is carried out for commercial purposes, it should be considered as production on an industrial scale, and the entire IVDR must be fulfilled.

Specialization in infrastructure may be an aspect to consider, e.g.:

- Procedures for material sourcing, manufacturing, quality control (QC), release, storage, logistics
- Supplier qualification and control
- Having in place defined production planning based on proactive assumptions for future demand (forecast)
- Defined quality assurance and product release criteria and deviation documentation
- Separating manufacturing from quality control
- Documentation of lot manufacturing and quality control
- Stockholding/warehousing system
- Storing retained sample

National competent authorities in EU member states are ultimately responsible for enforcing compliance with all requirements of the IVDR, including whether the device being manufactured or used by the health institution on its territory is being manufactured on an industrial scale.

3.11 How do you determine the risk class of the IHD?

Short answer
Annex VIII of the IVDR must be followed.

Explanatory information
The health institution must determine the risk class of the IHD considering its intended purpose and applying the most suitable classification rule stipulated in Annex VIII IVDR. MDCG Guidance 2020-16 provides further guidelines and examples on appropriate classification of IVDs [4].

4 Requirements for IHDs under Article 5.5 IVDR

4.1 What are the requirements for IHDs under Art. 5.5?

Short answer
Health institutions that manufacture, modify, or use IVD products in-house must operate under a quality management system (QMS), justify the use of the exemption, ensure and declare that the device fulfills the General Safety and Performance Requirements of Annex I IVDR, compile documentation describing design, manufacturing, and performance (for class D IHDs), monitor the clinical performance of the device and initiate corrective actions, if necessary, and last but not least, make information about the IHD publicly available.

Explanatory information
Health institutions wishing to manufacture, modify, or use IVD products in-house must ensure that:

- Products meet the relevant General Safety and Performance Requirements stipulated in Annex I IVDR.
- An appropriate quality management system is in place.
- Standard "EN ISO 15189 Medical laboratories — Requirements for quality and competence and national accreditation provisions" or other national provisions are followed.
- There is a justification for applying the exemption.

Note: Labs should regularly evaluate the justification and must define the time period appropriately, e.g., every 3 years.

- For class D IHD: Documentation of the design, manufacturing, performance, and intended purpose is compiled and on request can be made available to National Competent Authority.

Note: National legislation may extend this requirement to all device classes, e.g., in Germany.

- A declaration is in place that the IHD meets the applicable requirements.
- Experience gained from clinical use is reviewed, and, if necessary, corrective actions are performed.
- Selected information about the IHD is made publicly available.

Furthermore, the health institutions must consider any specific national provisions in the EU member states related to Art. 5.5.

4.2 What are the requirements stipulated in Annex I IVDR?

Short answer
Annex I of the IVDR contains so-called General Safety and Performance Requirements (GSPR) for IVD devices. The health institution must demonstrate and document that the IHD is in conformity with the applicable GSPR defined in Annex I.

Explanatory information
Annex I General Safety and Performance Requirements is divided into three chapters:

I. General Requirements

This chapter describes the requirement to establish a risk management system and the regular update of the benefit-risk ratio assessment. Risk assessment includes not only risks related to patients, but also risks to the users as well as risks related to use errors.

Note: Consulting the standard "EN ISO 14971 Medical devices - Application of risk management to medical devices" or "EN ISO 22367 Medical laboratories—Application of risk management to medical laboratories" may be helpful in this area.

II. Requirements regarding Performance, Design and Manufacture

This chapter describes requirements regarding design, manufacturing, characteristics, verification, validation, and performance of devices and is relevant for IHD. Health institutions should carefully check which requirements apply to their IHDs, since this is the basis for establishing the proof that there is no equivalent CE-marked device available.

III. Requirements regarding information supplied with the device

This chapter defines requirements for the information that is supplied with the device, product label, and instructions for use. The majority of the provisions in this chapter do not apply to IHD (e.g., attaching the CE marking). However, information relevant to safely use the device in accordance with its intended purpose must be followed, e.g.:

– Instructions for operating product
– Information on substances or mixtures which may be considered as being dangerous
– Expiry or manufacturing date
– Storage and handling conditions
– Batch or serial number

Health institutions are not required but may use standards or common specifications to demonstrate conformity with the corresponding GSPR, as IVD manufacturers do.

If a requirement is deemed not applicable to an IHD, the health institution should justify it. For example, IHDs that do not incorporate materials of biological origin do not need to demonstrate compliance with that requirement.

Health institutions should properly document and regularly update the proof of compliance of the IHD with the relevant GSPRs. This documentation contains critical information that will be used by competent authorities as a basis to assess compliance of an IHD with Article 5.5. Additionally, critical changes made to the IHD should be evaluated and documented.

Note: It is not explicitly required by the MDCG Guidance 2023-1 [5], but if a requirement is deemed not applicable to an IHD, it is advisable that the health institution should justify it. For example, IHDs that do not incorporate materials of biological origin do not need to demonstrate compliance with that requirement.

4.3 What is required regarding documentation under Art. 5.5 (g)?

Short answer
For Class D IHDs: Health institution is obliged to compile documentation on manufacturing facility and process, design, and performance data, and intended purpose of the IHD.

For class A, B, and C IHDs: Health institution must follow the national provisions on documentation requirements in the EU member state where it is based.

This documentation may be controlled by the national competent authority.

Explanatory information
The documentation required per Art. 5.5 (g) must allow the competent authority to understand the manufacturing process, design, and performance data, and intended purpose of the IHD. The documentation must be sufficiently detailed to enable the competent authority to ascertain that the general safety and performance requirements set out in Annex I of the IVDR are met.

On request, the technical documentation must be provided to the responsible national competent authority for compliance verification.

In accordance with Art. 5.5 (g) IVDR, the requirement to draw up the documentation applies to class D IHDs only. However, each EU member state may extend it to lower risk classes or specific product groups (e.g., in Germany drawing up technical documentation may be required per ordinance for all risk classes). Thus, the health institution must verify and follow the respective national legislation of their EU member state in addition to the EU IVDR Art. 5.5 (g). [5]

All information in the documentation should be presented in a clear, organized, readily searchable, and unequivocal way and must be kept up to date.

The following aspects should be considered in the documentation for IHDs, as far as applicable (non-exhaustive list included in MDCG 2023-1 [5]):

- **Manufacturing facility:** description of the infrastructure, the services and the work environment needed to safely manufacture the IHDs in a way that fulfils the product requirements, listing of the equipment that is essential for production, etc.
- **Manufacturing process:** explanation of the manufacturing processes, including a description of the raw materials, control of suppliers, final product testing, etc.

- **Intended purpose of the IHD:** specification of indications and contraindications, the patient target group or groups, function and/or information provided by an IHD (e.g., screening, monitoring, diagnosis, etc.), what type of specimen is used, etc.
- **Design:** principles of operation of the IHD and its mode of action, technical specifications including chemical, physical, and biological properties, list of applied standards, common specifications, and guidelines essential to meet the relevant general safety and performance requirements in Annex I IVDR, etc.
- **Performance data:** According to Annex I of the IVDR, IHDs shall be designed and manufactured in such a way that they are suitable regarding the performance they are intended to achieve. The generally acknowledged state of the art should be considered. Where applicable, a description of the analytical and clinical performance data supporting the intended purpose should be provided.

The health institution may refer to Annex II of the IVDR for further guidance on content.

4.4 What is required regarding public declaration under Art. 5.5 (f)?

Short answer
The health institution must issue a declaration that the IHD fulfills the general safety and performance requirements (GSPR) and must make it publicly available. National legislation must be considered.

Explanatory information
The health institution must issue a declaration similar to the declaration of conformity issued by (legal) manufacturers under the IVDR.

This declaration must contain the following information:

- Name and address of the health institutions,
- Identification of the IHD (e.g., name, reference code or number, intended purpose, ...), and
- A statement that the IHD meets the general safety and performance requirements set out in Annex I of the IVDR. If an applicable GSPR or parts thereof are not fulfilled, the declaration must also contain a justification.

The health institution must make this declaration publicly available (e.g., on its webpage).

The IVDR doesn't define the details regarding this declaration and its publication. However, the MDCG guidance on IHD [5] provides a template for what the declaration could look like (see Annex A of that guidance).

Health institutions should consider national legislation regarding rules or guidance on the exact declaration format, language, and publication requirements that must be fulfilled (e.g., publication on a dedicated webpage from the national competent authority).

Health institutions should regularly review their public declarations and update them, if necessary. [5]

4.5 What is required regarding the justification for manufacturing of the IHD according to Art. 5.5 (d)?

Short answer
The health institution must examine the market and draw up a written justification that the specific patient's needs cannot be met or cannot be met at the appropriate level of performance by an equivalent CE-marked device available on the local market.

The relevant national legislation and/or guidance must be considered.

Explanatory information
The IVDR doesn't provide details on the justification, but the MDCG guidance contains the following interpretative guidelines on this requirement: [5]:

Target patient group's specific needs

Target patient group should be understood as a group of patients who have in common the same disease, condition, or characteristics that could benefit from using the IHD.

The term "specific needs" should be understood as:

- A need for a specific in-vitro diagnostic medical device (in context of the definition of an IVD provided in Article 2.2 IVDR), or
- A specified level of performance covered by the IHD for certain performance characteristics.

Examples:

- The IHD covers a pediatric population while the CE-marked IVD does not.
- A more-sensitive method is needed for a specific patient group compared with the general population, for which a commercial CE-marked IVD is sufficient.
- The IHD combines the analysis of two or more CE-marked IVDs, reducing the amount of specimen necessary for testing a specific patient group.
- Test has better performance than the CE-marked IVD (faster results, higher precision, less interference).

Availability on the market

Market should be understood in this context as the local market of CE-marked devices that are accessible to the health institution according to national rules and regulations.

Equivalence of devices in the context of the justification

Equivalence of devices is not defined in the IVDR. However, some of the equivalence characteristics provided in the EU MDR can be used for the justification. In this context, equivalence can be based on technical, biological, or clinical aspects:

- **Technical equivalence:** e.g., the device is of similar design (e.g., antibody principle), is used under similar conditions, has similar specifications and properties including physicochemical properties, uses similar deployment methods, has similar principles of operation and critical performance characteristics.
- **Biological equivalence:** e.g., the device uses the same materials or substances with the same specimen (human tissues or body fluids) for a similar kind and duration of contact, has similar release characteristics of substances, including degradation products and leachable.
- **Clinical equivalence:** e.g., the device is used for the same clinical condition or purpose, including similar severity and stage of disease, in a similar population, has a similar relevant critical performance in view of the expected clinical effect for a specific intended purpose.

Thus, the justification that there is no equivalent device on the market could refer to different intended purposes, clinical conditions, patient groups, conditions of use, principles of operation, approved specimen materials, critical performance characteristics, or critical technical specifications. The justification of non-equivalence should be documented and regularly reviewed.

4.6 Are health institutions required to have a process for drawing up and reviewing the justification according to Art. 5.5 (d)?

Short answer
Yes, the Guidance MDCG 2023-1 [5] requires this.

Explanatory information
In accordance with the Guidance MDCG 2023-1 [5], the health institution should establish a process for searching the market if there are equivalent CE-marked devices for the specific patient needs.

For this purpose, the local medical device database, or the European database (EUDAMED) could serve as one of the sources of information to identify available CE-marked alternatives. For class C and D IVDs, the summary of safety and performance containing relevant device information is publicly available in EUDAMED and may be used for this purpose.

Other sources of information could be information from manufacturers, distributors, scientific conferences, etc.

Based on the search results, the health institution should draw up the justification for why the target patient group's specific needs cannot be met or cannot be met at the appropriate level of performance by an equivalent CE-marked device available on the market.

It is not sufficient to perform this search only once; the health institution should continue gathering information about the availability on the market of potentially equivalent CE-marked devices to consider market developments. Thus, the health institution should define the timelines for reviewing its justification on a regular basis.

Once the IHD is in use, possible subsequent availability on the market of an equivalent CE-marked device does not invalidate the initial justification for manufacturing. However, in such a case, the health institution should review and update its justification and initiate the transition to use the CE-marked product and stop manufacturing and using the IHD.

4.7 What is an appropriate quality management system (QMS) in the context of Art. 5.5 (b) IVDR?

Short answer
The health institution must establish and implement a QMS that is suitable and appropriate for the manufacturing, modification, and use of IHDs. Article 10.8 IVDR can be used as a basis for this task.

Note: Compliance with EN ISO 15189 or equivalent national provisions only is not sufficient to fulfill this requirement. Relevant national legislation and/or guidance must be considered.

Explanatory information
The IVDR doesn't provide details on the scope and content of the QMS in the context of Art. 5.5 (b) IVDR. The MDCG Guidance 2023-1 [5] provides further clarification on this topic.

Per Art. 5.5 (c), the medical laboratory must be also compliant with standard EN ISO 15189 or, where applicable, national provisions, including accreditation and certification. However, compliance with EN ISO 15189 or equivalent national provisions alone is not sufficient to fulfill the requirements of Article 5.5 (b) IVDR on QMS.

Article 10.8 of the IVDR describes the minimum aspects that a QMS for manufacturing of CE-marked IVDs can use as a basis, as applicable to IHDs. In addition, relevant harmonized standards concerning manufacturing (EN ISO 13485) or risk management (EN ISO 14971 or EN ISO 22367) can be considered.

Therefore, the MDCG guidance advises that Art. 10.8 IVDR describing the relevant requirements on manufacturer's QMS can be taken as a basis by the health institutions to establish an appropriate QMS, e.g.,:

- **Compliance with Art. 5.5 and Annex I of the IVDR**
  Healthcare institutions must define processes for fulfilling the requirements of Article 5.5 and to identify and fulfill the applicable general safety and performance requirements of Annex I IVDR. In addition, a process for drawing up and publishing the declaration confirming compliance of the IHD with Annex I IVDR must be established.
- **Responsibility of the management**
  According to Article 5.5 (h), the health institution must ensure that all IHD are manufactured in accordance with Art. 5.5 and, where applicable, with the documentation referred to in Article 5.5 (g). The QMS should also include processes for management of resources.
- **Risk management**
  The health institution must establish a process to establish, implement, document, and maintain a risk management system.

  The risk management system is a continuous iterative process that should cover the entire lifecycle of the IHD, requiring regular systematic updating and cover the elements defined in Annex I, point 3.

  Note: The health institution may take the harmonized standard EN ISO 14971 and EN ISO 22367 as a basis for establishing an appropriate risk management system.
- **Identify, generate, and appraise data**
  The health institution shall establish a process to gain, analyze, and document supporting data to justify that the target patient group´s specific needs cannot be met or cannot be met at the appropriate level of performance in another way than by manufacturing and using the IHD.

  The QMS should also cover a process for obtaining information about equivalent CE-marked devices that become available on the market.

  Furthermore, a process for gaining and analyzing experience from clinical use of the IHD and defining and implementing necessary measures (e.g., corrective actions), where necessary. (Article 5.5 (d), (g) and (i)).

- **Manufacturing**
  For class D IHDs (and for other risk classes if required by national provisions):

  The health institution must establish a process to draw up appropriate documentation on the manufacturing process, design, performance data, and intended use of the IHD. (Article 5.5 (g)).

- **Traceability**
  The health institution shall implement an appropriate process that allows the identification and traceability of the IHD, e.g., to identify affected IHDs and involved patients and implement required corrective actions.

  For labeling Annex I, Chapter III of the IVDR describing labeling requirements for CE-marked IVDs shall be considered as applicable for the IHDs. (Article 5.5 (f) (ii), IVDR Annex I, Chapter III, Article 5.5 (i)).

- **Monitoring, analysis, and continuous improvement**
  The health institution shall establish a process to review experience gained from clinical use of the IHD and define all necessary corrective actions (Article 5.5 (i)).

- **Communication with competent authorities**
  The health institution must be prepared to answer to requests of its competent authority and provide it with required information and documentation. (Article 5.5 (e), (g))

In addition, relevant harmonized standards concerning manufacturing (EN ISO 13485) or risk management (EN ISO 14971 or EN ISO 22367) can be considered by the health institution.

The QMS can cover the whole health institution or only parts thereof that are involved in the manufacturing and/or modification.

4.8 What information about IHDs must be made publicly available?

Short answer
The health institution must disclose publicly its name and address, details that identify the IHD, and a declaration that the IHD meets the requirements stipulated in Annex I of the IVDR. Additional national rules must be followed.

Explanatory information
There are public information requirements for IHDs. The health institution is required to make the following information about an IHD publicly available (Art 5.5 f):

- Name and address of the manufacturing health institution
- Details strictly necessary to identify the IHD
- A declaration that the IHD meets the requirements stipulated in Annex I of the IVDR. This includes information and reasoned justification on requirements that are not met.

Health institutions should follow additional national legislation, rules, or guidance regarding the exact format, language requirements, and the publication conditions of the declaration (e.g., publication on the health institution's website and/or on a dedicated webpage from the competent authority).

The Guidance MDCG 2023-1 [5] provides a template for the public declaration in Annex A.

Health institutions should regularly review their public declarations and update them if necessary.

4.9 What is required regarding vigilance, incidents, and corrective actions under Art. 5.5 (i)?

Short answer
Health institutions must gain and review experience from clinical use of the IHDs and, if necessary, conduct corrective actions.

Explanatory information
Health institutions should have a documented procedure in place to collect and analyze data from the clinical use of the IHDs, process incidents, and implement corrective actions. There are no additional details provided on this topic in the IVDR Art. 5.5 nor in MDCG 2023-1 [5].

Health institutions should consider national legislation on possible additional requirements regarding reporting of incidents and corrective actions to competent authorities.

4.10 What is the timeline for the application of the different provisions of Article 5.5?

Short answer
Art. 5.5 (a) applies from May 26, 2022

Art. 5.5 (b), (c) and (e) to (i) apply from May 26, 2024

Art. 5.5 (d) applies from May 26, 2028

Explanatory information
Article 113.3 (i) and (j) define the following application dates for the requirements of Article 5.5:

- Point (a) *transfer of IHD to another legal entity:* shall apply from May 26, 2022 = no additional transition time is granted.
- Point (b), (c) and (e) to (i) *implementation of QMS, compliance with ISO 15189, providing information to competent authority, publish public declaration, compiling documentation for class D IHD, review experience from clinical use:* shall apply from May 26, 2024, = 2 years additional transition are granted.
- Point (d) *justification:* shall apply from May 26, 2028 = 6 years additional transition are granted.

4.11 Why is a longer transition time granted to health institutions to comply with the Art. 5.5 IVDR?

Short answer
Due to the COVID pandemic, health institutions need more time for the implementation of the new rules for in-house devices.

Explanatory information
Except for the general safety and performance requirements laid down in Annex I of the IVDR, IHDs are exempted from the IVDR, provided the health institution meets several conditions set out in Article 5.5 of the IVDR. Among other things, health institutions must have an appropriate quality management system, comply with the international standard setting out the quality and competence requirements for medical laboratories (EN ISO 15189) or other national provisions, and justify that the target patient group's specific needs cannot appropriately be met by an equivalent in vitro diagnostic medical device available on the market.

Since the outbreak of the pandemic, many health institutions, in particular hospitals, have had to focus their efforts on dealing with COVID-19. The transition for most of the conditions to be met by health institutions making IHDs has been extended until May 26, 2024. The requirement for the justification that there is no equivalent CE-marked device available to meet the target patient group's specific needs is deferred even further, until May 26, 2028, as health institutions will need an overview of CE-marked IVDs available on the EU market to comply with this requirement.

5 Other questions related to Article 5.5 IVDR

5.1 Who is responsible for enforcement of Article 5.5?

Short answer
European National Competent Authorities based in the individual member states.

Explanatory information
The National Competent Authorities established in the EU member states are responsible for the implementation and enforcement of the IVD Regulation, including Art 5.5.

5.2 What kind of information can be requested from health institutions by competent authorities?

Short answer
Upon request from the national competent authority, the health institution shall provide comprehensive information and documentation on the manufacture, use, modifications, clinical performance, and production volume of IHDs, as well as the justification in accordance with Art. 5.5 (d). In addition, national legislation must be considered.

Explanatory information
Specifically, the following information/data may be requested by the national competent authority from the health institution:

- General information, e.g., device type, intended use, target patient group
- Data on the design, safety, performance, and expected benefit from the device
- Justification that there are no equivalent CE-marked alternatives on the market to meet the target patient group's specific needs
- Description of the manufacturing process and performed modifications
- Information regarding use of the IHD (e.g., procedures, combination with other devices, data on compatibility)
- Number of units or batches manufactured and a justification of the production volume
- Data regarding the performance of the device in routine use (e.g., performance data, incidents, complaints, corrective actions) undertaken

In addition, the health institution should check if there are any specific national provisions related to notifying the competent authority, e.g., when an IHD is put into service, modified, or discontinued.

5.3 Is there an EU-wide guidance in place for health institutions on how to implement the requirements of Art. 5.5?

Short answer
Yes, the MDCG 2023-1 [5].

Explanatory information
A dedicated working group composed of the EU Commission and representatives from all EU members states elaborated a European implementation guidance providing interpretations related to the requirements for health institutions that wish to manufacture, modify, and use IHDs as stipulated in Art. 5.5 of the IVDR. However, there can be more-specific national provisions in place in the EU member states regarding Art. 5.5 that must be considered by health institutions.

In addition, the International Standardization Organization (ISO) is currently working on a new standard pertaining to IHDs: ISO 5649 "Concepts and specifications for the design, development, production and use of in-house in vitro diagnostic medical devices (laboratory-developed tests)" that may be considered once available.

5.4 Must IHDs bear a CE marking?

Short answer
No.

Explanatory information
Per Art. 18 of the IVDR, only devices that are not intended for performance studies and are in conformity with the requirements of the IVDR shall bear the CE marking of conformity. IHDs are exempted per Art. 5.5 and consequently may not bear the CE marking.

5.5 Must health institutions register IHDs in the European database (EUDAMED)?

Short answer
No.

Explanatory information
There is no obligation in Art. 5.5 for health institutions to register IHDs in EUDAMED. However, local registration requirements in EU member states may apply.

5.6 Is Unique Device Identification (UDI) required for IHDs?

Short answer
No.

Explanatory information
There is no obligation in Art. 5.5 for health institutions to assign UDI to IHDs.

5.7 Can health institutions commercialize IHDs?

Short answer
Yes, but the entire IVDR must be fulfilled, and the device must be CE-marked.

Explanatory information
If the health institution decides to commercialize the IHD, it can no longer benefit from the exemption stipulated in Art. 5.5 and must fulfill the entire IVDR and CE-mark the device accordingly.

However, nothing prevents the health institution from charging a fee for the use of an IVD that it manufactures and uses.

5.8 Can health institutions use research use only (RUO) products for the development of IHDs?

Short answer
Yes, but in this case, the health institution must ensure that the requirements of Art. 5.5 are fulfilled for the product.

Explanatory information
A product intended for research use only (RUO) is not intended to be used for a medical or diagnostic purpose. The health institution must use the CE-marked IVD for any examinations and processes, provided these are available and suitable to meet the patient's needs. Should the clinical needs remain unmet, there is no limitation on any product category that the health institution can use to develop an IHD, e.g., RUO, provided that the requirements of Article 5.5 of the IVDR are fulfilled.

5.9 What is considered a modification or minor/major change to an existing IVD, which means that it becomes an IHD?

Short answer
There is no specific information in the IVDR regarding what is considered a modification or minor/major change of an IVD in the context of Art. 5.5. However, in general, any significant deviations from manufacturer's instructions for use that alter the function, safety, performance, or intended purpose of the device can qualify as a modification or change, e.g., adding a new or changing the existing intended purpose of the device, changing or adding specimens.

Explanatory information
Under the IVDR, there are explicit requirements for the content of the intended purpose (including specifying e.g., specimens, function, targeted population, etc.). The intended purpose and clinical use must be explicitly supported by the device's performance evaluation; also, other general safety and performance requirements must be met. Therefore, the technical documentation and labeling must make the intended purpose of the device clear and define how the device should be used, etc.

Notably, health institutions are specifically permitted to modify and use devices in-house to cover unmet patient needs (Recital 29) and receive an exemption from most of the IVDR requirements other than Annex I and Article 5.5 IVDR, if the respective criteria for the IHD exemption are met.

Examples:

- Change in specimen type: An organ transplantation center adapts a CE-marked Epstein Barr virus test designed for use on venous blood, so that it can be used to screen an organ for the virus. The organ transplantation center is responsible for validating the change in specimen.
- Use of a product for research use only for medical diagnostic purposes: A lab uses products intended for life science research, such as antibodies for IHC staining of tissue biopsies. The laboratory is responsible for validation of the antibodies as an IVD.
- Change in assay protocol and laboratory workflow: The laboratory pools samples to shorten turnaround time and simplify the workflow. In case of a positive result, testing will be repeated for the affected samples. Pooling may affect sensitivity or specificity (e.g., dilution of viral load). The health institution must validate the change in assay protocol.
- Test for the quantification of creatinine in belly urine, not externally collected urine, leading to the other reference ranges of the protein but also to other interferences due to presence of other infiltrated proteins (example from EU clinical chemistry lab association).

A note on misuse: This can be considered an off-label use where the natural or legal person does not assume the obligations incumbent on the manufacturer as a result of altering or using the device differently than its intended purpose (including, in some cases, in spite of a limitation by the manufacturer in the instructions for use, e.g., "do not use the device [a blood glucose self-test] for the purpose of monitoring gestational diabetes"). This would also apply where a health institution modifies a device or uses it off-label without taking responsibility for doing so and meeting the requirements under either Article 5.5. or CE marking under the IVDR.

5.10 Are there any liability issues for IVD manufacturers that provide components, ingredients, or support to health institution to develop IHD?

Short answer
The health institution is liable for the IHD. However, in this case, the IVD manufacturer is considered a supplier and is liable in this role for the quality of materials or services provided to the health institution as stipulated in the contractual agreement between both parties.

Explanatory information
The manufacturer is liable regarding damage caused by defective IVDs that it has CE-marked (IVDR Art 10.15). The manufacturer is also presumed responsible and liable for claims it makes for its device, and it is not allowed to promote any product claims not covered by the instructions for use. Except for items that are specifically intended to replace a part or a component of a device (Art. 20), the IVDR does not regulate the provision of components (unless these qualify as a device in their own right), nor does it govern potential liability arising from such provision. According to Annex I, 20.4, the labeling of these materials must accurately describe the contents and the use, e.g., individual reagents such as primers to detect specific gene sequences, etc.

6 References

1. European Regulation (EU) 2017/746 on in vitro diagnostic medical devices
2. European Directive 98/79/EC on in vitro diagnostic medical devices
3. IMDRF PMD WG/N49 FINAL: 2018 Definitions for Personalized Medical Devices
4. MDCG 2020-16 Guidance on Classification Rules for in vitro Diagnostic Medical Devices under Regulation (EU) 2017/746
5. MDCG 2023-1 Guidance on the health institution exemption under Article 5(5) of Regulation (EU) 2017/745 and Regulation (EU) 2017/746
6. MDCG 2022-6 Guidance on significant changes regarding the transitional provision under Article 110(3) of the IVDR

7 Annex 1: Relevant legal references within the IVDR

7.1 Preamble

(28) To ensure the highest level of health protection, the rules governing in vitro diagnostic medical devices, manufactured, and used within a single health institution only, should be clarified and strengthened. That use should be understood to include measurement and delivery of results.

(29) 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. In that context, it is appropriate to provide that certain rules of this Regulation, as regards devices manufactured and used only within health institutions, including hospitals as well as institutions, such as laboratories and public health institutes that support the health care system and/or address patient needs, but which do not treat or care for patients directly, should not apply, since the aims of this Regulation would still be met in a proportionate manner. It should be noted that the concept of 'health institution' does not cover establishments primarily claiming to pursue health interests or healthy lifestyles, such as gyms, spas, wellness, and fitness centers. As a result, the exemption applicable to health institutions does not apply to such establishments.

7.2 Article 2. Definitions

(29) "'Health institution' means an organization the primary purpose of which is the care or treatment of patients or the promotion of public health;"

(2) 'in vitro diagnostic medical device' means 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) concerning a physiological or pathological process or state;

(b) concerning congenital physical or mental impairments;

(c) concerning the predisposition to a medical condition or a disease; (d) to determine the safety and compatibility with potential recipients;

(e) to predict treatment response or reactions;

(f) to define or monitoring therapeutic measures.

Specimen receptacles shall also be deemed to be in vitro diagnostic medical devices;

(4) 'accessory for an in vitro diagnostic medical device' means an article which, whilst not being itself an in vitro diagnostic medical device, is intended by its manufacturer to be used together with one or several particular in vitro diagnostic medical device(s) to specifically enable the in vitro diagnostic medical device(s) to be used in accordance with its/their intended purpose(s) or to specifically and directly assist the medical functionality of the in vitro diagnostic medical device(s) in terms of its/their intended purpose(s);

7.3 Article 5.5 Placing on the market and putting into service

Article 5. Section 5

"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 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.

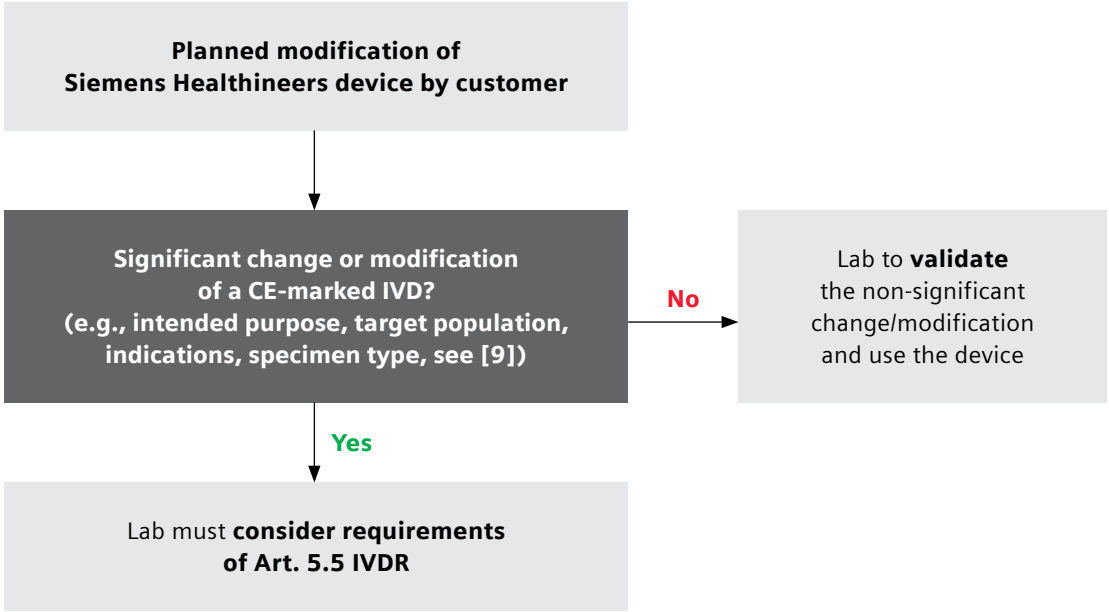
(h) the health institution takes all necessary measures to ensure that all devices are manufactured in accordance with the documentation referred to in point (g); and

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

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."

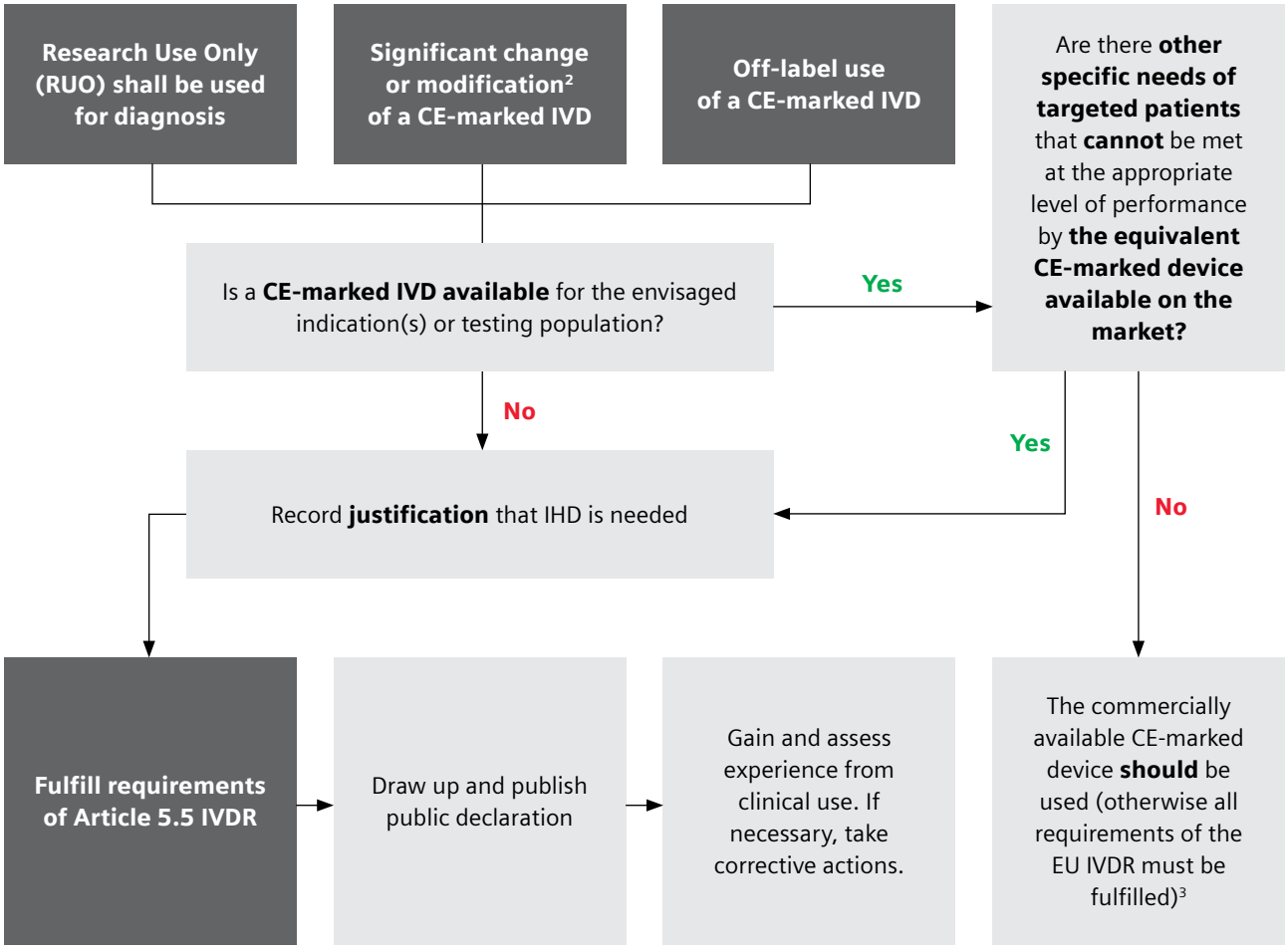
This paragraph shall not apply to devices that are manufactured on an industrial scale.

8 Annex 2: Flowchart "Assessing modifications of CE marked IVDs"



9 Annex 3: Flowchart "What could fall under the IHD requirements?

Healthcare institution **manufactures, modifies, or uses** devices **in-house** on a **non-industrial scale** to address the **specific needs of a target patient group** that **cannot be met** at the appropriate level of performance[1] by an **equivalent device available on the EU market.**



1. Critical feature may include e.g., specific patient needs or population, device functionality, performance, reliability, etc.

2. Significant change or modification may include but is not limited to e.g., design change, change of intended purpose, specimen type, changing or adding indications for use, changing/adding testing population, change to the performance claims, change to critical raw material, software patches that add functionalities to the interpretation of assay results, etc. MDCG Guidance 2022-6 may be useful for this assessment [6].

3. If a lab significantly changes or modifies a CE-marked device that doesn't qualify as an IHD and may NOT benefit from the exemption of Art. 5.5, all requirements of the IVDR must be fulfilled (not only those of Art. 5.5 IVDR).

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