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Guidance on qualification of *in vitro* diagnostic medical devices

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Introduction

The purpose of this guidance document is to clarify what products fall in scope of Regulation 2017/746 on *in vitro* diagnostic medical devices (IVDR) – also referred to as 'qualification' as an *in vitro* diagnostic medical device (IVD) or an accessory to an IVD. In order to be qualified as an IVD or an accessory to an IVD, the product must fulfil the definition in Art 2(2) or Art 2(4) of the IVDR respectively. The qualification depends on the intended purpose as described by the manufacturer.

The demarcation between the IVDR and Regulation (EU) 2017/745 on medical devices (MDR) is of particular importance because the MDR lays down in its article 1 that it shall not apply to *in vitro* diagnostic medical devices (IVDs).

The present guidance document provides non-exhaustive lists of examples of IVDs and accessories to IVDs. Further detailed examples may be found in the Manual on Borderline and Classification in the Community Regulatory framework for medical devices. The reader could also find it useful to consult MDCG 2019-11 "Guidance on Qualification and Classification of Software in Regulation (EU) 2017/745 – MDR and Regulation (EU) 2017/746 – IVDR". Both documents are published on the European Commission website[1].

The examples provided are indicative and the qualification of specific products should be considered on a case-by-case basis by each manufacturer based on their intended purpose. Thus, products detecting or measuring the same analyte could be qualified differently, depending on the intended purposes as assigned by each manufacturer.

1. General principles of qualification

In deciding on whether a product falls within the scope of the IVDR, the primary considerations are the provisions and definitions set out in Articles 1 and 2 of the IVDR.

1.1. Definitions of a medical device and an *in vitro* diagnostic medical device (IVD)

Article 2 (2) of the IVDR defines an IVD as:

"'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.

[1] See Medical Device Coordination Group guidance documents here: https://health.ec.europa.eu/medical-devices-sector/new-regulations/guidance-mdcg-endorsed-documents-and-other-guidance_en#sec1

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

Article 2(1) of the MDR defines a medical device as:

"'medical device' means any instrument, apparatus, appliance, software, implant, reagent, material or other article intended by the manufacturer to be used, alone or in combination, for human beings for one or more of the following specific medical purposes:

- *diagnosis, prevention, monitoring, prediction, prognosis, treatment or alleviation of disease,*
- *diagnosis, monitoring, treatment, alleviation of, or compensation for, an injury or disability,*
- *investigation, replacement or modification of the anatomy or of a physiological or pathological process or state,*
- *providing information by means of in vitro examination of specimens derived from the human body, including organ, blood and tissue donations, and which does not achieve its principal intended action by pharmacological, immunological or metabolic means, in or on the human body, but which may be assisted in its function by such means.*

The following products shall also be deemed to be medical devices:

- *devices for the control or support of conception;*
- *products specifically intended for the cleaning, disinfection or sterilisation of devices as referred to in Article 1(4) and of those referred to in the first paragraph of this point."*

1.2 Essential characteristics of an IVD

The essential characteristics of an IVD are that:

a) An IVD can be a **reagent, reagent product, calibrator, control material, kit, instrument, apparatus, piece of equipment, software or system**.

Animals used for diagnostic purposes, e.g. dogs used for detection of cancer are not IVDs.

b) The IVD may be intended to be used either **alone or in combination** with other devices or products.

c) The IVD is used ***in vitro*[2] for the examination of a specimen** derived from the human body.

The specimen is never reintroduced into the body.

Note: if no specimen is involved, or if the examination takes place in or on the human body (*in vivo*), the devices intended to be used for this examination are not IVDs (see section 2.2.2 and 2.3).

d) The IVD is used *in vitro* for the examination of a specimen derived from **the human body**.

Devices for detection of pathological agents in the environment or in animals (e.g. detection of *Borrelia* in the tick that has bitten a patient to aid the diagnosis of Lyme disease) or devices used in veterinary diagnostics (e.g. for the detection of SARS-CoV-2 or cancer in canines or bovine spongiform encephalopathy in cows) are not IVDs.

e) The principal intended purpose of an IVD is to solely or principally **provide information for** one or more medical purposes as follows:

[2] In this context, *'in vitro'* means not in contact with the human body.

Information:	Examples:
Concerning a physiological process or state	e.g. devices intended for detection of menopause, ovulation or pregnancy
Concerning a pathological process or state	e.g. a self-test for HIV screening, devices for screening or staging of cancer, device for identification of IgG antibodies against *Helicobacter pylori*
Concerning congenital physical or mental impairments	e.g. devices intended for evaluating the risk of trisomy 21, device intended for newborn screening for congenital hypothyroidism, severe combined immunodeficiency (SCID) or spinal muscle atrophy (SMA)
Concerning the predisposition to a medical condition or disease	e.g. devices intended for detection of lactose or gluten intolerance, devices intended for detecting genetic carriers of cystic fibrosis, devices intended to detect genetic alterations of the *BRCA1* gene for hereditary breast cancer
To determine the safety and compatibility with potential recipients	e.g. devices intended for ABO system blood grouping, or HLA typing
To predict treatment response or reactions	e.g. devices intended for screening of the *HLA-B*5701* allele to determine the risk of hypersensitivity to abacavir in HIV-infected individual, devices intended for *SLCO1B1* variants to predict statin-induced myopathy, devices intended for determining principal gene variants of *MTHFR* to identify patients with a reduced activity of enzyme MTHFR who are at increased risk of serious adverse events in patients treated with methotrexate
To define or monitor therapeutic measures	e.g. devices intended for monitoring of blood glucose levels, devices intended for T-helper cells to monitor therapeutic measures, devices intended for measuring the levels of digitoxin

According to Article 2(12) of the IVDR, the *'intended purpose' means the use for which a device is intended according to the data supplied by the manufacturer on the label, in the instructions for use or in promotional or sales materials or statements or as specified by the manufacturer in the performance evaluation.*

A product might have several intended purposes. If at least one of these intended purposes is to provide information for a medical purpose as outlined in Article 2(2) IVDR, then the product must comply with the requirements of the IVDR before the manufacturer can place it on the market. For example, a kit intended by its manufacturer for lay users to reveal their ethnic origins as well as their predisposition to certain diseases should be qualified as an IVD and should therefore comply with the IVDR.

Products without a medical purpose (as outlined in Article 2(2) IVDR) are not IVDs. Examples: tests to determine ancestry, to find relatives, or to reveal ethnic origins, or tests intended to be used for sport, wellbeing and lifestyle purposes

Note: products cannot be brought into the scope of the IVDR merely by mentioning IVD or 'for *in vitro* diagnostic use'.

2. Specific qualification topics

2.1. Accessories

Article 1(1) of the IVDR states that: *"This Regulation lays down rules concerning the placing on the market, making available on the market or putting into service of* in vitro *diagnostic medical devices for human use and accessories for such devices in the Union."*

Article 2(4) of the IVDR defines an accessory as *"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)".*

Example: a cleaning solution specifically intended by its manufacturer to be used with a defined automated IVD instrument is an accessory of the instrument.

2.2. Specimen receptacles and products used for the collection of specimens

2.2.1. Specimen receptacles

Article 2(2) of the IVDR states that:

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

Article 2(3) of the IVDR states that:

"'Specimen receptacle' means a device, whether vacuum-type or not, specifically intended by its manufacturer for the primary containment and preservation of specimens derived from the human body for the purpose of in vitro diagnostic examination."

Notes:

(a) the word "primary" does not necessarily refer to the initial or first container of the specimen in point of time, but rather to a container that is intended by its manufacturer to mainly come into direct contact with the specimen and which could therefore affect the specimen, and

(b) the word "preservation" does not imply that the receptacle has to contain a specimen preservative, but that the receptacle is intended to protect the specimen, for example, from temperature fluctuations, from light, from physical breakage, from contamination etc.

It is possible that more than one specimen receptacle is involved in the collection, transport and storage of an individual specimen. In such cases the manufacturer of each receptacle must have evidence of compliance with the IVDR.

Examples*:* Blood collection tubes, urine or stool specimen containers, are considered to be IVDs. Blood bags intended to store blood with the aim of later introduction into the body are considered to be medical devices, not IVDs.

Products that come into direct contact with the human body should be handled as described in sections 2.2.2.b and 2.6.2.

Other glass or plastic tubes, cups, cuvettes or other receptacles into which the specimen is placed during the analytical process (by aliquoting or otherwise), are not considered to be 'specimen receptacles' within the meaning of the IVDR unless they are specifically intended by their manufacturer to be used for *in vitro* diagnostic examination, e.g. as an accessory. They are usually considered to be general laboratory equipment.

2.2.2. Products used for the collection of specimens

a) Without intended direct contact with the human body

A product intended to transfer the specimen, but which is not specifically intended by its manufacturer for the primary containment and preservation of specimens derived from the human body for the purpose of *in vitro* diagnostic examination, should not be qualified as an IVD (e.g. plastic pipettes to transfer blood drop from finger to measuring device).

b) With intended direct contact with the human body

Invasive (within the meaning of the MDR) specimen collection devices or those which are directly applied to the human body for the purpose of obtaining a specimen must not be considered to be accessories to *in vitro* diagnostic medical devices (Article 2(4) IVDR). These products are regarded as medical devices within the scope of the MDR.

Examples: needles, lancets, lancing devices, mouth tubes, swabs, urine collection bags, sweat cards placed in direct contact with the skin and intended to be used as part of a system to measure chloride ions in sweat for the diagnosis of cystic fibrosis.

2.3. Devices where no specimen is involved

Some diagnostic medical devices function without the need of a containable specimen taken from the patient.

The definition of an *in vitro* diagnostic medical device states that IVDs are "intended by the manufacturer to be used in vitro for the examination of specimens, *derived from the human body*". Therefore, if no specimen is *'derived from the human body'* the device should not be qualified as an IVD. Such products should be qualified as medical devices.

Note that standalone software can fall within the scope of the IVDR, when it is intended to provide information based on results from other IVDs, although it does not analyse the human specimens directly (see section 2.8).

Examples:

A non-invasive device intended for the detection of blood glucose by energy emission (e.g. near infra-red energy) on the human body should not be qualified as an IVD but is a medical device.

A pulse oximeter intended to measure the oxy/deoxyhaemoglobin ratio by passing light through the fingertip and absorbing infrared light should not be qualified as an IVD but as a medical device.

An MRI scanner should not be qualified as an IVD but as a medical device.

2.4. Products for general laboratory use

Article 1(3)(a) of the IVDR states that the IVDR does not apply to:

"products for general laboratory use or research-use only products, unless such products, in view of their characteristics, are specifically intended by their manufacturer to be used for in vitro diagnostic examination."

Where, on the basis of its characteristics, the manufacturer specifically intends its product to be used for *in vitro* diagnostic examination, the product becomes an IVD or an accessory of an IVD and must comply with the applicable requirements of the IVDR.

If, however, the product for general laboratory use does not possess specific characteristics that makes it suitable for one or more identified *in vitro* diagnostic examination procedures, then the manufacturer should not qualify the product as an IVD. Merely adding the statement "for *in vitro* diagnostic use" to a product is not sufficient to qualify a product as an IVD.

Products for general laboratory use utilised *in vitro* in the preparation of specimens that have been obtained for examination (e.g. paraffin, stains) are considered neither as IVD nor as accessories and fall outside the scope of the IVDR unless such products, in view of their characteristics, are specifically intended by their manufacturer to be used for *in vitro* diagnostic examination or fulfil the definition of an accessory.

Examples of products for general laboratory use and IVDs (non-exhaustive):

	General laboratory use product	**Covered by IVDR[3]**
Centrifuges	General centrifuges, cytospin	Hematocrite centrifuge
Pipettes	General purpose pipettes (e.g. single or multiple pipettes, plastic pipettes, Pasteur pipettes)	Blood coagulation pipettes with automatic timing (accessory for coagulometer)
Tubes and flasks	Erlenmeyer flasks, general plastic tubes	Blood collection tubes, urine specimen containers
Plates	General empty ELISA plates, general empty Petri dishes	Coated microtiter plates for the diagnosis of Lyme disease
Nucleic acid extraction products	DNA and RNA extraction/purification kits that only extract/purify nucleic acids	DNA and RNA extraction kits intended to prepare an extract to be used with a specific IVD device or if specifically intended to be used for in vitro diagnostic examination

[3] If the manufacturer's intended purpose is such that it fulfils the definition of an IVD.

General equipment	Scales, balances, microtomes, incubators, sterilizers for laboratory equipment, paraffin embedding machine, water baths, ELISA plate washers	
HPLC products	Size-exclusion HPLC columns	HPLC columns for IVD purposes: e.g. HbA1c
PCR machines	General PCR machine	PCR machine intended for IVD purposes: e.g. detection and differentiation of influenza/SARS-CoV-2 RNA
Detection equipment	Mass spectrometers, spectrophotometers, ELISA readers providing raw data which is not readily readable and understandable by the user (e.g. peaks, OD).	McFarland bacteria density reader specifically intended for IVD examination of human specimens
Others	Foetal calf serum, cell culture media, fixation solution, mounting media, buffers (e.g. PBS), chemicals (e.g. sulphuric acid, formol, water)	Wash solution intended to be used with a specific IVD analyser, culture media intended for amplification and detection of infectious agents in human specimens

2.5. Products for research use only

Recital (7) and Art.1(3)(a) of IVDR state that the IVDR does not apply to Research Use Only (RUO) products.

Products intended for research use only cannot be intended by their manufacturers for a medical purpose (as outlined in Article 2(2) IVDR).

2.6. Combinations of products placed on the market together

2.6.1 IVD kits

The definition of an IVD includes 'kit' as being an IVD in itself.

Article 2(11) of the IVDR states that:

"'kit' means a set of components that are packaged together and intended to be used to perform a specific in vitro diagnostic examination, or a part thereof."

A set of components that are packaged together may be treated as a kit under the IVDR if the intended purpose of the set of components as a whole, as defined by the manufacturer of the kit, falls within the definition of an IVD. IVD kits should be CE marked in themselves on the outer packaging and fulfil the requirements regarding the 'information supplied by the manufacturer' (IVDR, Annex I, Chapter III.20).

A kit with an intended purpose falling within the definition of an IVD may contain:

a) Only IVDs and accessories (e.g. antibody, antigen, coated ELISA plates, specimen receptacles), which may be either:
   - CE marked, in case the IVDs are also made available as separate devices; or,
   - not individually CE marked;

b) a combination of IVDs and:
   - medical devices (e.g. lancet, swab), which must be CE marked in accordance with the MDR[4];
   - other products, such as products for general laboratory use (e.g. pipette for transferring a patient specimen);
   - food products (e.g. chewing gum added for inducing a patient reaction in order to obtain a specific specimen).

Note: IVD kits may not include medicinal products. Where an IVD is intended to be used with a medicinal product and the products are packaged together, this combination may not be qualified as an IVD kit. Each product must comply with its corresponding legislation. [5]

Example: Product intended for collection of exhaled air for subsequent detection of *Helicobacter pylori* consisting of labelled urea (a medicinal product) to be ingested, a straw (a medical device) and a specimen container (an IVD). The entire co-packaged product cannot be qualified as an IVD kit.

Note: Article 2(10) MDR states that: *"'procedure pack' means a combination of products packaged together and placed on the market with the purpose of being used for a specific medical purpose.*" The qualification either as a 'procedure pack', according to the MDR or as a 'kit' according to the IVDR should be based on the intended purpose of the whole product combination. A procedure pack should not have an intended purpose that corresponds to Article 2(2) IVDR. A procedure pack must contain at least one medical device. If the whole product combination is qualified as a procedure pack, it should comply with the requirements set in the MDR. IVD components that are included in a procedure pack should fulfil the requirements of the IVDR.

2.6.2 Devices incorporating, as an integral part, a medical device

IVDR Art 1(4) states:

"Any device which, when placed on the market or put into service, incorporates, as an integral part, a medical device as defined in point 1 of Article 2 of Regulation (EU) 2017/745 shall be governed by that Regulation [i.e. the MDR]. *The requirements of this Regulation* [i.e. the IVDR] *shall apply to the* in vitro *diagnostic medical device part."*

The same concept is referred to in MDR Art 1(7).

[4] During the transition period provided for in Art 120 MDR, medical devices CE marked in accordance with the MDD may also be part of an IVD kit.

[5] See also Question 1.1 in Questions & Answers document for applicants, marketing authorisation holders of medicinal products and notified bodies with respect to the implementation of the Regulations on medical devices and in vitro diagnostic medical devices (Regulations (EU) 2017/745 and (EU) 2017/746): https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/questions-answers-implementation-medical-devices-vitro-diagnostic-medical-devices-regulations-eu-2017-745-eu-2017-746_en.pdf

An integral product consists of at least two constituent parts, one of which is an IVD, and the other is a medical device, which are physically combined in such a manner that they form a single object.

Examples:

- A device involving the vacuum suction of saliva into the integrated handle of a device which contains reagent material (e.g. for the detection of HIV) should be qualified as a medical device and not as an IVD.
- Swabs with integrated reagents should be qualified as medical devices and not as IVDs.
- A continuous in vivo glucose monitoring device measuring glucose in interstitial fluid, with an integrated in vitro measurement function on capillary blood specimens, should be qualified as a medical device and not as an IVD.
- A specimen transport tube with a swab integrated into the cap should be qualified as a medical device and not as an IVD.

The following are not considered integral products, i.e. the medical device and IVD components are qualified separately and must respect the requirements of the MDR and IVDR respectively:

- medical devices packaged together with an IVD without forming a single object (see section 2.6.1), e.g. a specimen collection kit with a specimen receptacle and a separate swab;
- detachable medical devices packaged together with an IVD (see section 2.6.1), e.g. a urine receptacle to which a detachable funnel can be attached which is held against the body;
- medical devices only referenced in the instructions for use of an IVD.

2.7. Calibrators and control materials

According to Article 2(2), calibrators and control materials can be IVDs provided that they satisfy the definition of an IVD.

The IVDR provides the following definitions in Article 2(55) and (56):

"'calibrator' means a measurement reference material used in the calibration of a device;"

"'control material' means a substance, material or article intended by its manufacturer to be used to verify the performance characteristics of a device;"

According to Article 1(3)(c) and (d), internationally certified reference materials and materials used for external quality assessment schemes are not considered IVDs.

If External Quality Assessment (EQA) organisations make available these EQA materials for an intended use which falls in scope of the IVD definition in Article 2(2) of the IVDR, for example as control materials or calibrators, outside of the scope of EQA schemes, these materials are considered as IVDs. In that case, EQA organisations would be considered as manufacturers and the products must be CE marked under the IVDR.

2.8. Software

According to Article 2(2) of IVDR, software can fall within the scope of the IVDR. For further guidance on qualifying software as either an IVD software or a medical device software, please consult MDCG 2019-11[6].

2.9. Microbiological culture media

In order to be qualified as an IVD, the culture media or components of culture media (e.g. in powder form) must be specifically intended by the manufacturer to provide information concerning a physiological or pathological state, on specimens derived from the human body.

Such qualification for culture media includes elements that should be, according to IVDR requirements, available to the user, in particular:

- the type of information provided by the IVD (presence, characteristics and typing of micro-organisms) for medical purposes;
- indication of the appropriate type of human specimens required (e.g. blood or urine).

Example**:** general microbiological culture media containing a selection agent like MacConkey Agar and CLED Agar can be an IVD or not depending on the intended purpose specified by a manufacturer.

2.10. Stains

In order to be qualified as IVD, stains used in histology, cytology and microbiology (e.g. for smears and tissue sections) must be intended to provide information concerning a physiological or pathological state on specimens derived from the human body.

Such qualification of stains includes elements that should be, according to IVDR requirements, made available to the user, in particular:

- the type of information provided by the IVD for medical purposes (characteristics and performance of the stains, specific identification by the stains);
- indication of the appropriate type of human specimens required.

Example: Ziehl-Neelsen Stain can be an IVD or not depending on the intended purpose specified by the manufacturer.

A stain without any specific medical intended purpose should not be qualified as an IVD.

2.11. Tests intended to be used in manufacturing process control

Tests used to monitor the manufacturing of products, such as medicinal products should not be qualified as IVDs as they do not have a medical purpose as outlined in the IVDR.

Example: A test used to detect an infectious agent in plasma intended for the manufacturing of an advanced therapy medicinal product should not be qualified as an IVD.

[6] See: https://health.ec.europa.eu/system/files/2020-09/md_mdcg_2019_11_guidance_qualification_classification_software_en_0.pdf

2.12. Tests intended to be used in the context of biological or chemical warfare

Tests for detection of agents of biological or chemical warfare in the environment should not be qualified as IVDs because they are not intended to be used on human specimens.

If, however, one of the intended purposes of such a test is the *in vitro* examination of human specimens with a medical purpose, it should be qualified as an IVD.

2.13. Tests to be used in law enforcement

Tests intended to be used only in the course of law enforcement or for other nonmedical purposes, for example paternity tests or tests for detecting abuse of alcohol or drugs, should not be qualified as IVDs.

If, however, the *in vitro* examination of human specimens with a medical purpose is one of the intended purposes of a specific product, the IVDR will apply.

2.14. Relation with Regulation (EU) No 528/2012 on biocidal products

Products falling within the scope of the IVDR are excluded from the scope of Regulation (EU) No 528/2012. However, when a biocidal product falls within the scope of the IVDR and is intended to be used for other purposes not covered by the IVDR, the biocides Regulation also applies to that biocidal product insofar as those purposes are not addressed by the IVDR (Article 2(2) of the biocides Regulation).