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GUIDELINES ON MEDICAL DEVICES

IVD GUIDANCES : Borderline issues

A GUIDE FOR MANUFACTURERS AND NOTIFIED BODIES

Note

The present Guidelines are part of a set of Guidelines relating to questions of application of EC-Directives on medical devices. They are legally not binding. The Guidelines have been carefully drafted through a process of intensive consultation of the various interest parties (competent authorities, Commission services, industries, other interested parties) during which intermediate drafts were circulated and comments were taken up in the document. Therefore, this document reflects positions taken by representatives of interest parties in the medical devices sector.

IN VITRO DIAGNOSTIC MEDICAL DEVICES: BORDERLINE ISSUES

Foreword

The present Guideline is part of a set of Guidelines relating to questions of application of EC-Directives on *In Vitro* Diagnostic Medical Devices. They are not legally binding. The Guideline has been carefully drafted through a process of intensive consultation of the various interested parties (Competent Authorities, Commission Services, Manufacturers and other interested parties in both the IVD and the Medical Device sectors) during which intermediate drafts were circulated and comments were taken up in the document. Therefore this document reflects positions taken in particular by the aforementioned interested parties.

Due to the participation of the aforementioned interested parties, including experts from Competent Authorities, it is anticipated that these guidelines will be followed within the Member States and, therefore, ensure uniform application of relevant Directive provisions.

1. Introduction

This guideline should be read in association with the scope of Directive 98/79/EC as stated in article 1 (2) and with particular reference to an *in vitro* diagnostic medical device (IVD)¹ having a 'medical purpose', and in relation to Directive 93/42/EEC concerning medical devices. The guideline provides a practical support for the uniform application of these Directives. It deals with specific issues in the context of the Directives and is therefore of complementary nature to the 'Guide to the implementation of directives based on the New Approach and the Global Approach'. The aim is to establish the demarcation between both legal regimes. The document also aims to provide guidance in relation to issues that have arisen in relation to other Directives e.g. Medicinal Products and Biocides or other non-IVD products.

One of the main borderline issues that will arise is the determination of the borderline between the *In Vitro* Diagnostic Medical Devices Directive (IVDD) and the Medical Devices Directive (MDD). This determination is of fundamental importance because the two directives are mutually exclusive.² A product cannot be an IVD under

¹ IVD in this document should be read as *in vitro* diagnostic medical devices in the sense of European Directive 98/79/EC.

² There will inevitably be difficult borderline cases, but the following factors indicate why it is essential to determine whether a particular device is within the scope of the MDD or that of the IVDD:-

- the essential requirements and the conformity assessment procedures of the MDD were developed and adopted on the basis that that Directive would not apply to IVDs and they are therefore different from those that were eventually developed specifically taking into account the particular nature of IVDs and their users.
- unlike the IVDD, the MDD contains no provision for the development and adoption of common technical specifications and therefore devices falling within the scope of the MDD cannot be required to comply with any such quasi-mandatory specifications;
- harmonised standards published for the purposes of the IVDD would not give rise to the legal presumption of compliance as regards devices that fall within the scope of the MDD and *vice-versa*;
- notified bodies designated only for the purposes of the MDD will not have (or are unlikely to have) competence in the field of IVDs and certainly any competence that they may have in that field will not have been assessed by the designating competent authority and *vice-versa*.

Directive 98/79/EC and a medical device under Directive 93/42/EC as the two directives are mutually exclusive. A product can only be under one or the other directive. This is so because, during the development of the MDD, it was decided to develop a Directive establishing the legal regime for the free movement IVD medical devices later and separately and, consequently, Article 1.5 of the MDD specifically states that that directive does not apply to IVD medical devices. Although the legal regime that was eventually developed for application to IVD medical devices was in the form of a new approach directive and followed very closely the general structure of the MDD, the IVDD contains many significant differences especially as regards the essential requirements (including the labelling requirements)³ and the conformity assessment procedures.

2. Definitions, essential characteristics and medical purpose

2.1 Definitions

A product is an IVD device, if it fulfils the clauses a) and b) of the Article 1.2 of Directive 98/79/EC:

1. intended use and properties as a medical device according to Article 1.2 a) and
2. intended use and properties as a IVD device according to Article 1.2 b)

* thus a product must firstly be determined to be a medical device before determining whether or not it is an IVD, within the definitions contained in the directive 98/79/EC.

Reference is made in this guidance document to the following relevant definitions, namely:

“medical device” -	Article 1.2(a) of the MDD and of the IVDD
“in vitro diagnostic medical device” -	Article 1.2(b) of the MDD (as amended by Directive 98 / 79 / EC) and of the IVDD
“specimen receptacle” -	Article 1.2(b) of the IVDD
“accessory” -	Article 1.2(c) of the IVDD
“intended purpose” -	Article 1.2 (h) of the IVDD

2.2 Essential Characteristics

The essential characteristics of an IVD, whether consisting of a single component or a combination, are that:

- > its principal intended purpose is to provide information
 - concerning a physiological or pathological state or
 - concerning a congenital abnormality or
 - to determine the safety and compatibility with potential recipients or
 - to monitor therapeutic measures,
- > the device is used *in vitro* for the examination of a specimen derived from the human body, and
- > the information thus obtained is to be used for one or more of the medical purposes specified in Article 1.2 (a, b).

2.3 Medical Purpose

In order for a product to come within the scope of the Medical Device Directives (including the IVDD) it must be intended by the manufacturer to be used for a medical purpose. If no medical purpose is intended by the manufacturer then the product is not a medical device. Thus the intended purpose for a product will be key in determining whether or not the product is a (IVD) medical device.

³ the labelling requirements of the MDD were developed without reference to the special nature and characteristics of IVDs and without reference to the specialised information needs of their professional and lay users;

It is to be noted that Article 1.2 (h) of the IVDD provides that the “intended purpose” is the use for which a device is intended according to the data (presumably, the information) supplied by the manufacturer on the labelling, in the instructions for use and / or in promotional material.

Examples:

- *Devices for detection of agents of biological or chemical warfare in the environment are not IVD’s because such products have no medical purpose. On the other hand a device intended to be used on human specimens in the detection of biological or chemical warfare agents with medical purpose would fall within the scope of the IVDD (see point 9).*
- *Devices intended to be used only in the course of law enforcement or other non-medical purposes, for example for detecting drugs of abuse/alcohol, are outside the scope of the IVDD (see point 10).*
- *If however, the in- vitro examination of human specimens with a medical purpose is one of the intended uses of a specific product, the IVD Directive will apply.*
- *A product for research use only which has no medical purpose, cannot be a medical device and, therefore, cannot be an IVD medical device. By definition, these products fall outside the scope of the IVDD and the other medical devices directives.*

3. Specimen receptacles

Article 1.2(b) of the IVD Directive clearly states that specimen receptacles are considered as IVD’s. It defines specimen receptacles for this purpose as those devices that are specifically intended by the manufacturer to be for the primary containment and preservation of specimens derived from the human body for the purposes of in vitro diagnostic examination. This applies whether the product is vacuum type or not.

This specific intended use should be included on the labelling and any associated promotional literature for the product. The manufacturer must also have evidence and technical documentation to support this use for the product. A manufacturer cannot place the CE mark on a piece of general laboratory equipment as a marketing claim, without ensuring that it complies with all the relevant essential and other requirements of the directive and have evidence to substantiate this.

It is possible for more than one specimen receptacle to be 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 directive as above.

During the actual analytical process the receptacles into which the specimen is placed (by aliquoting or otherwise), may be glass or plastic tubes, cups, cuvettes or other receptacles. These are unlikely to be ‘specimen receptacles’ as defined in the directive. They are usually considered to be general laboratory equipment, however in some cases they could be considered accessories to an IVD.

In the context of the definition of “specimen receptacle” in Art. 1.2 (b), of the IVD Directive it should be noted that:

- (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 one intended to protect the specimen, for example, from temperature fluctuations, from light, from physical breakage, etc.

Example:

Sample tubes, microbial transportation devices (tubes). Article 1 (2) b applies.

Note: Specimen receptacles that come into contact with a patient are considered to fall within the scope of the MDD and not the IVDD.

Accessory

Note: The second paragraph of the definition of “accessory” in Art 1.2 (c) of the IVDD states that invasive sampling devices or those which are directly applied to the human body for the purpose of obtaining a specimen within the meaning of Directive 93/42/EEC are not to be considered as accessories to IVD’s. Thus, for example, where a manufacturer’s kit includes lancets or pricking devices to obtain a blood specimen, they are to be regarded as being devices within the scope of the MDD and not accessories to the IVD.

4. Products for general laboratory use

Products for general laboratory use (non-IVD products) are not IVD’s unless on the basis of its specific characteristics the manufacturer specifically intends such products to be used for in vitro diagnostic purposes. Thus such a product must possess specific characteristics to make it suitable for in vitro diagnostic procedures in order to be classified as an IVD.

Products used in vitro in the preparation of samples that have been obtained for examination, but not used directly in the actual test can be considered to be IVD’s if the manufacturer specifically states that the product can be used for in vitro diagnostic purposes, otherwise they fall outside the scope of the directive.

The one qualification provided for in the Directive is where, on the basis of its characteristics (emphasis added), a manufacturer specifically intends that the product should be used for *in vitro* diagnostic examination. In this case, the product becomes an IVD and must comply with the applicable essential and other requirements of the IVDD and must be CE marked. If, however, the product does not in fact possess specific characteristics that make it suitable for one or more identified *in vitro* diagnostic examination procedures, then the manufacturer is not free to bring it within the scope of the IVDD merely by affixing the CE marking to it. In other words, a manufacturer is not able to bring within the scope of the IVDD a product that, in reality, is a piece of general laboratory equipment simply by affixing the CE mark to it.

Example:

Laboratory products that are not usually considered to fall within the scope of the IVD directive include: sterilizers, laboratory centrifuges, general purpose automatic pipette, weighing machines, microtomes, multi purpose tubes, pipettes and flasks etc. where such items have no specifically intended in vitro diagnostic use. Examples also include items for general purpose use such as foetal calf serum, culture media and stains, unless the manufacturer’s intended purpose falls within the definition of an in vitro diagnostic medical device.

5. Products for research use only

A product for research use only which has no medical purpose, cannot be a medical device and, therefore, cannot be an IVD medical device. By definition, these products fall outside the scope of the IVDD and the other medical devices directives.

Recital 8 of Directive 98/79/EC states:

Whereas instruments, apparatus, appliances, materials or other articles, including software, which are intended to be used for research purposes, without any medical objective, are not regarded as devices for performance evaluation.

This means that products for research purposes, which have no medical indication and are not yet established in medical diagnosis, are excluded from the scope of the directive.

6. Devices for IVD purposes with an invasive body contact

Some devices may incorporate both specimen collection and analytical functions. These devices may be 'borderline' between the Medical Device Directive 93/42/EC and the IVD Directive 98/79/EC. Borderline cases such like this should be approached with regard to the principal intended purpose of the product. Thus if the principal intended purpose is for the product is to be used in vitro for the examination of specimens derived from the human body for the purposes of providing information the IVD directive would apply. (Art 2b).

Devices which during their measuring function involve contact with the human system (as defined in 93/42/EEC Annex IX) in order to obtain a continuous sample are not considered to be IVD devices.

Example:

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). The use of such a device involves the penetration of the device into a body orifice for the collection of the specimen and this may appear to make it a medical device within the scope of the MDD. However, its principal intended purpose is the provision of relevant information by the in vitro examination of the specimen derived from the patient. The device's brief contact with the patient or penetration into the patient's body to collect the specimen is subsidiary and incidental to its principal intended purpose.

Mouth and other swabs having integrated reagents or reagent areas are IVD's because their principal intended purpose is to provide information relevant to the medical purposes specified in Article 1.2 (b).

The intended purpose, invasiveness and continuity of sampling are important criteria in deciding the correct regulatory route for this kind of product.

Example:

A "Holter" blood glucose monitoring system that includes a subcutaneous catheter to provide a continuous supply of the patient's specimen to an in vitro analysing instrument is a medical device not an IVD because, during the in vitro measuring function, surgically invasive contact with the patient is necessary in order to obtain a continuous specimen flow. In this case, the analytical function is carried out at the same time as the continuous specimen collection process is still going on. There is no dissociation of the specimen from the patient and therefore the analytical function cannot properly be regarded as being "in vitro". Such a device would therefore be a medical device within the scope of the MDD. Other examples are continuous pH measurements during haemodialysis and oxygen saturation devices.

Other Sampling Devices (also see pt. 3)

Sampling devices which are either invasive (needles, lancets etc) or that come into contact with patients, that are made available together with IVD devices (in kits, procedure packs etc) are not considered to be accessories to IVD devices, They come within the scope of the MDD and have to be CE marked as medical devices.

Note: For devices that have key features, which could be considered as being covered by the MDD as well, the relevant requirements (e.g. biocompatibility, sterility, etc.) of that directive need to be considered during the conformity assessment procedure.

7. Kits containing IVD's and medicinal products

Medicinal products made available together with IVD devices are to be authorised for marketing by the normal process for medicinal products and the primary, and if applicable the secondary packages of the medicinal products are to be labelled according to the rules for medicinal products. The IVD components of the "kits" themselves fall within the scope of the IVD Directive and must therefore comply with its requirements and carry the CE mark, but will not need not be authorised for marketing as medicinal. This also applies to any MDD components. I.e. each set of

regulatory requirements needs to be met for each of the individual medicinal products, medical device and/or IVD medical device components.

Example:

A Helicobacter pylori breath test kit containing labelled urea (a licensed pharmaceutical product) to be ingested prior to sampling for analysis, a straw (a medical device) and a sample container (an IVD).

Note: So far as the medicinal product is concerned, it must have been granted a marketing authorisation covering the actual use for which it is being included in the IVD kit and it must be labelled in accordance with the regulations relating to medicinal products. The IVD component of the kit must comply with all the applicable essential and other requirements of the IVDD (including the labelling requirements) and it must bear the CE marking. It is important to note that, while the CE marking of the IVD content of the kit entitles it to free movement within the European Economic Area (subject to language requirements), that is not so as regards the medicinal product. That aspect must be considered separately under the relevant medicinal product legislation as must the extent to which the label of the kit must provide information about the medicinal product over and above a statement that the kit contains the medicinal product.

8. Control Materials

Some EQA organisations distribute materials for internal control, national calibration materials, etc. These materials are IVD's and must bear the CE label.

	CE Label	Remarks
Calibrators/Controls included in the kit	Part of the kit	Calibrators and controls with assigned values must be traceable
Standing alone calibrators and internal quality control (IQC) materials (assigned or not assigned) Even if these materials are also used as EQA materials ⁴	CE label	Calibrators and controls with assigned values must be traceable
Specific EQA materials	No CE label	Reference Recital (9) of 98/79/EC
Reference material of higher order	No CE label	Metrological traceability required

9. Devices where no specimen is involved

Some medical diagnostic devices function without a specimen is being taken from the patient. Since it is an essential part of the definition of an *in vitro* diagnostic medical device that the manufacturer's intention is that the product should be used "... for the examination of specimens...", it follows that a medical device that functions without the need for a patient specimen cannot be an IVD within the scope of the IVDD. Such products will almost always be a medical device within the scope of the MDD.

Example

A non-invasive medical device for the detection of blood glucose by energy emission (e.g. near infra-red energy) is not an IVD because no specimen derived from the human body is involved, but it would be a medical device for the purposes of the MDD.

⁴ This part of the table is still subject to discussion and can be changed in the next revision of this Meddev (3 Nov 2003)

10. Devices involved in biological or chemical warfare

Devices for detection of agents of biological or chemical warfare in the environment are not IVD's because such products have no medical purpose. A device used on human specimens with medical purpose in the detection of biological or chemical warfare agents would be an IVD.

11. Devices to be used in law enforcement

Devices intended to be used only in the course of law enforcement or other non-medical purposes, for example paternity tests or tests for detecting drugs of abuse/alcohol, are not IVD's. If however, the *in vitro* examination of human specimens with a medical purpose is one of the intended uses of a specific product, the IVD Directive will apply.

12. Boundary with the Biocides Directive 98/8/EC

IVD's according to the Directive 98/78/EC shall be exempted from the Biocides Directive (amendment not accomplished yet).

Note: Biocidal substances used as a raw material in an IVD may have to fulfil the requirements of the Biocides directive as well⁵.

⁵ This part of the text is still subject to discussion and can be changed in the next revision of this Meddev (3 Nov 2003)