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GUIDELINES ON MEDICAL DEVICES
IVD Medical Device Borderline and Classification issues
A GUIDE FOR MANUFACTURERS AND NOTIFIED BODIES

Foreword

The present Guideline is part of a set of Guidelines relating to questions of application of EC Directives on medical devices.

This guideline is not legally binding, since only the European Court of Justice can give an authoritative interpretation of Community law. It has been elaborated by an expert group including experts from Member States' Competent Authorities, the Commission' services, as well as industry trade associations. It is therefore intended that the document will provide useful guidance which should assist common positions to be taken throughout the European Union. Due to the participation of the aforementioned interested parties and of experts from Competent Authorities, it is anticipated that these guidelines will be followed within the Member States and, therefore, ensure the uniform application of relevant Directive provisions.

The present guideline provides non-exhaustive lists of examples of IVD medical devices, accessories to IVD medical devices and medical devices. Further detailed examples may be found in the Manual on Borderline and Classification in the Community Regulatory framework for medical devices, published on the European Commission website¹.

Note: This document is a revision of an earlier document published in January 2004 as MEDDEV 2.14/1 rev 1.

¹ http://ec.europa.eu/health/medical-devices/documents/borderline/index_en.htm

CONTENT
Introduction
Part A – Qualification
1. General principles of qualification
1.1. Definition of an IVD medical device
1.2. Accessories
1.3. Specimen receptacles and products used for the collection of specimens
1.3.1. Specimen receptacles
1.3.2. Products used to obtain specimens
1.4. Products for general laboratory use
1.5. Products for research use only
1.6. IVD kits
1.7. Control Materials
2. Specific cases on qualification
2.1. Microbiological culture media
2.2. Stains
2.3. Devices with an invasive body contact for IVD purposes
2.4. Devices where no specimen is involved
2.5. Devices involved in biological or chemical warfare
2.6. Devices to be used in law enforcement
2.7. Relation with the Biocides Directive 98/8/EC
Part B – Classification
1. General principles on Classification

1.1. Interpretation of annex II, list A

1.1.1. Interpretation of “marker of infection” wording

1.1.2. Clarification of “rare” blood groups and subgroups

1.2. Interpretation of annex II, list B

1.2.1. Classification of Chlamydia detection IVD medical devices

1.2.2. Classification of in vitro diagnostic kits measuring parameters which can be used for evaluating the risk of trisomy 21

IN VITRO DIAGNOSTIC MEDICAL DEVICES: BORDERLINE ISSUES

1. Introduction

The demarcation between the IVD Medical Device Directive 98/79/EC (IVDD), on the one hand, and other sectoral legislation, on the other hand, in particular the Medical Device Directive 93/42/EC (MDD), is crucial for the proper implementation of these Directives and the correct interpretation and enforcement of national laws.

In particular, the qualification of a product as an IVD or as a medical device will have an impact on:

- the essential requirements and the conformity assessment procedures to be followed,
- the appropriate technical specifications giving presumption of conformity (common technical specifications and harmonised standards),
- the selection of a competent designated notified body to conduct the conformity assessment procedure.

The demarcation between the IVDD and the MDD is of fundamental importance because the MDD foresees in its article 1 that this Directive shall not apply to IVD medical devices.

Therefore, it was recognised that the subject needs to be further explained and illustrated by practical guidance.

Part A - Qualification

1. General principles of qualification

In deciding on whether a product falls within the scope of the IVD Directive, the primary consideration are the definitions set up in article 1 (2) of Directive 98/79/EC.

1.1. Definition of an IVD

Article 1(2) (b) of the IVDD 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, equipment, 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:

— 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 essential characteristics of an IVD are that:

1. The principal intended purpose of an IVD is to **provide information on** one or more of the following medical purposes:

- * information concerning a physiological state e.g. menopause assay, ovulation assay, pregnancy test or
- * information concerning a pathological state e.g. HIV assay
- * information concerning a congenital abnormality e.g. evaluation of the risk of trisomy 21
- * to determine the safety and compatibility with potential recipients e.g. determination of blood groups of the ABO system
- * to monitor therapeutic measures e.g. digitoxin assay

Note that tests for detecting drugs abuse/alcohol, intended to be used in law enforcement are not IVDs (see 2.6)

2. The IVD may provide this information either **alone or in combination** with other devices or products
3. The IVD is used ***in vitro* for the examination of a specimen** derived from the human body and where such specimen is never reintroduced into the body.

Note that 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 2.3 and 2.4)

Examples:

- a pulse oxymeter emitting light through the fingertip and absorbing infrared light, to measure the oxy/deoxyhemoglobin ratio is not an IVD,
- a continuous blood glucose monitoring system where the analytical function is carried out at the same time as the continuous specimen collection is not an IVD.

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

Note that devices for detection of e.g. pathological agents in the environment are not IVDs.

From the definition it follows that in order to be qualified as an IVD the product must first fulfil the definition of a medical device² and therefore must be intended by its manufacturer to be used for a medical purpose³.

According to Article 1.2 (h) of the IVDD, the *“intended purpose” means the use for which the device is intended according to the data supplied by the manufacturer on the labelling, in the instructions for use and/or in promotional materials.*

There may be cases where ‘claims’ of a medical nature are made for certain products where those claims cannot be substantiated by technical, clinical and scientific data. If there is insufficient clinical, technical and scientific data to support the claims made, the product does not meet the requirements of the MDD and therefore shall not be CE marked as a medical device or an IVD.

Products cannot be brought into the scope of the IVDD, merely by mentioning ‘for *in vitro* diagnostic use’.

On the other hand, a product might have several intended uses. If one of these intended uses is the *in vitro* examination of human specimens and if a medical purpose can be established based on sufficient and broadly agreed scientific, diagnostic and clinical evidence, then the product must comply with the requirements of the IVDD before the manufacturer can place it on the market.

Products cannot be placed on the market as “Research use only’ (RUO) products if these products have a medical intended purpose.

1.2. Accessories

Directive 98/79/CE, article 1.2 (c) defines an accessory as *“an article which, whilst not being an IVD, is intended specifically by its manufacturer to be used together with a device to enable that device to be used in accordance with its intended purpose”.*

Directive 98/79/CE, article 1.1 states that “This Directive shall apply to *in vitro* diagnostic medical devices and their accessories. For the purposes of this Directive, accessories shall be treated as *in vitro* diagnostic medical devices in their own right. Both *in vitro* diagnostic medical devices and accessories shall hereinafter be termed devices.”

Example: a cleaning solution specifically intended by its manufacturer to be used with a defined automated IVD instrument

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

1.3.1. Specimen receptacles

² It is to be noted that the definition of a medical device in Directive 98/79/EC is not strictly identical to the definition of a medical device set up in Directive 93/42/EEC. However the definitions of a medical device in both directives are considered to be similar

³ Further information regarding the interpretation of the medical purpose can be found in MEDDEV 2.1/1. (http://ec.europa.eu/health/medical-devices/files/meddev2_1-1_04-1994_en.pdf)

Article 1(2) (b) of the IVDD states that:

“Specimen receptacles are considered to be in vitro diagnostic medical devices.

‘Specimen receptacles’ are those devices, whether vacuum-type or not, specifically intended by their manufacturers 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, etc.

This specific intended use shall be clearly indicated 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.

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 IVDD.

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 IVDD. They are considered to be general laboratory equipment.

Examples:- Blood collection tubes, urine sample containers are considered as IVDs.

Specimen receptacles with an invasive body contact should be handled in the same way as described in chapter 1.3.2.b.

1.3.2. Products used to obtain specimens

a) Without intended direct contact with the human body

A product intended to transfer the sample, 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, is usually not considered to be an IVD (e.g. plastic pipettes to transfer blood drop from finger to rapid test)

b) With intended direct contact with the human body

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 shall not be considered to be accessories to *in vitro* diagnostic medical devices (Art 1.2.c) (e.g. needles, lancets, lancing devices, mouthtubes, swabs, urine collection bags for babies). These products are regarded as being devices within the scope of Directive 93/42/EEC.

1.4. Products for general laboratory use

Article 1(2) (b) of the IVDD states that:

“Products for general laboratory use are not in vitro diagnostic medical devices unless such products, in view of their characteristics, are specifically intended by their manufacturer to be used for in vitro diagnostic examination.”

The qualification provided for in the Directive is where, on the basis of its characteristics, 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 requirements of the IVDD and therefore must be CE marked.

If, however, the product does not possess specific characteristics that make it suitable for one or more identified *in vitro* diagnostic examination procedures, then the manufacturer is not allowed to qualify its product as an IVD. A manufacturer is not allowed to affix the CE mark on a piece of general laboratory equipment as a marketing claim. Merely adding the statement “for *in vitro* diagnostic use” to a product is not sufficient to qualify a product as an IVD.

Products used *in vitro* in the preparation of samples that have been obtained for examination are considered neither as IVD nor as accessories and fall outside the scope of the Directive unless, based on their characteristics, they are specifically intended for a particular IVD test. The validation of this specific combination shall be clearly documented in the technical documentation.

Examples of product of general laboratory use and IVD medical devices:

	Laboratory use product	Covered by IVD Directive
Centrifuges	General centrifuges, cytopsin	Hematocrite centrifuge
Pipettes	General purpose pipettes (e.g. single or multiple pipettes, plastic pipettes, Pasteur pipettes)	Blood coagulation pipettes with automatic timing (Accessory of coagulometer)
Tubes and flasks	Erlenmeyers, plastic tubes	Blood collection tubes, urine sample containers
Plates	Empty ELISA plates, empty Petri dishes,	Coated microtiter plates for the diagnosis of Lyme’s disease

Nucleic Acid extraction products	DNA and RNA extraction kits that only provide a specimen without an intended IVD detection combination	DNA and RNA extraction kits intended to provide a specimen to be used with an IVD device (validation for at least one combination is to be provided)
General equipment	Scales, balances, microtomes, incubators, sterilizers for laboratory equipment, paraffin embedding machine,	
HPLC products	size-exclusion HPLC columns	HPLC columns for IVD purposes: e.g. HbA1c
Detection equipment	Mass spectrometer, spectrophotometers, ELISA readers providing raw data which is not readily readable and understandable by the user (e.g. peaks, OD).	McFarland bacteria density testing
Others	Foetal calf serum, cell culture media, fixation solution, mounting media, buffers (e.g. PBS), chemicals (e.g. sulphuric acid, formol, water)	

(This table contains a non-exhaustive list of examples).

1.5. Products for research use only

For further guidance on RUO, please consult MEDDEV 2.14/2 rev.1: *IVD Guidance: Research Use Only products*⁴

1.6. IVD kits

The definition of an IVD includes 'kit' as being an IVD in itself. The IVDD does not give a definition of 'kit', but it is generally agreed that a 'kit' consists of more than one component that are made available together and intended to be used to perform a specific IVD examination.

A whole product combination, placed on the market as a single product, shall be treated as a 'kit' and fulfil the requirements of the IVDD, if the principal intended purpose of the whole product combination falls within the definition of an IVD.

The combined use of the products contained in the 'kit' shall be validated by the manufacturer of the kit during the conformity assessment procedure.

The 'kit' shall be classified and assessed for its conformity to the requirements of the IVDD, according to the principal intended purpose of the whole product combination and must be CE marked and labelled under the IVDD (Annex I, B, ER 8.4).

A 'kit' with a principal intended purpose falling within the definition of an IVD medical device may contain:

a) IVD medical devices (e.g. antibody, antigen, coated ELISA plates, specimen receptacles), which may be either:

- CE marked under the IVDD in their own right allowing them to be also marketed separately, or
- not CE marked,
- a combination of both CE marked and not CE marked.

b) a combination of IVD medical devices and :

- medical devices (e.g. lancet, swab), which must be CE marked according to Directive 93/42/EEC;
- other products, such as products for general laboratory use (e.g. pipette for transferring a patient sample), which shall not be CE marked;
- food products (e.g. chewing gum added for inducing a patient reaction in order to obtain a specific sample), which shall not be CE marked.

Note: while the CE marking of the kit ensures its free movement within the European Union (subject to language requirements), this is not automatically the case for medicinal products. This should be considered separately under the relevant medicinal product legislation.

⁴ http://ec.europa.eu/health/medical-devices/files/meddev/2_14_2_research_only_product_en.pdf

Note: the 'kit' shall fulfil in its own the requirements regarding the 'Information supplied by the manufacturer' (IVDD, Annex I,B,8) and must be CE marked, but shall not bear an additional CE marking on the outer packaging for the medical devices included in the kit.

Note: the qualification either as a 'procedure pack', according to MDD or as a 'kit' according to IVDD should be based on the *principal intended purpose* of the whole product combination. If the whole product combination is qualified as a 'procedure pack', this will comply with the requirements set in the Medical Device Directive 93/42/EEC. When IVD components are included in the procedure pack, they shall fulfil the requirements of the IVD Directive 98/79/EC.

1.7. Control Materials

	IVD	Remarks
Calibrators/Controls included in the kit	Kit is an IVD	Calibrators and controls with assigned values must be traceable
Stand alone calibrators/controls (either as part of a kit or provided separately) used to confirm/define the validity criteria of one or several IVD assay	IVD	Calibrators and controls with assigned values must be traceable If the control material includes control values for parameters listed in List A or List B of Annex II, the control material shall be classified according to the highest classification
Specific EQA materials including materials (stand alone calibrators) used for an external quality assurance system	Not IVD*	Reference Recital (9) of 98/79/EC
Reference material of higher order	Not IVD	Metrological traceability required

* When External Quality Assessment organisations make available these EQA materials for internal control, national calibration materials, etc, outside of the scope of EQA schemes, these materials are considered as IVD medical devices. In that case, EQA organisations would be considered as manufacturers and the products must be CE marked under the IVD Directive.

2. Specific cases on qualification

2.1. Microbiological culture media

In order to be qualified as an IVD, the culture media must be specifically intended, designed and validated 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 available to the user, such as:

- 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 (general or specific like blood or urine);
- any specific specimen collection, transport and storage requirements (e.g. sterile collection for blood culture);
- manufacturer batch release criteria.

Culture media without any specific medical intended purpose are not qualified as an IVD.

Powder culture media will also be considered as an IVD if the above mentioned conditions are fulfilled.

It should be noted that powder bulk components of microbiological culture media are not considered to fall under the scope of the IVD Directive.

2.2. Stains

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

Such qualification includes elements that should be made available to the user, such as:

- 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
- any specific specimen collection, transport, storage and preparation requirements

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

2.3. Devices with an invasive body contact for IVD purposes

Some devices may in a single product incorporate both specimen collection and analytical functions. These devices may be 'borderline' between the MDD and the IVDD because they are in contact with the body and/or are invasive. Their intended purpose is to be used for the examination of specimens derived from the human body for the purpose of providing information.

These borderline cases should be treated on the basis of their principal intended purpose. Thus, where the principal intended purpose of the product is to be used *in vitro* for the examination of specimens derived from the human body for the purposes of providing information according to the definition of an IVD, the IVDD would apply. In that case, due to the invasive characteristics of the IVD, special care has to be applied for essential requirements 1 and 2 of Directive 98/79/EC which include all risks for patients. In that respect, the respective essential requirements of MDD should be taken into account, namely the requirements regarding the sterility, biocompatibility and toxicity.

Devices which involve contact with the human body in order to **obtain continuous specimen collection** are not considered to be IVD.

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).

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). But in the case they are invasive, they have to fulfil the relevant essential requirements of the MDD.

If the swab doesn't include the measuring or detection function, it would be considered as invasive sampling device and therefore qualified as a medical device.

A continuous blood glucose monitoring system (Holter) that includes a subcutaneous catheter to provide a supply of the patient's specimen to an external analysing instrument is a medical device not an IVD because, during the *in vitro* measuring function, a 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. 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.

2.4. 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 IVD medical devices are “intended by the manufacturer to be used *in vitro* for the examination of specimens, *derived from the human body*”. Therefore, if no sample is ‘*derived from the human body*’ the device is not considered to be an IVD. Such products shall be qualified as medical devices.

Examples:

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 is a medical device within the scope of the MDD.

A pulse oxymeter emitting light through the fingertip and absorbing infrared light, to measure the oxy/deoxyhemoglobin ratio falls within the scope of the MDD. There is no specimen derived from the patient involved.

2.5. Devices involved in biological or chemical warfare

Devices for detection of agents of biological or chemical warfare in the environment are not IVD because they do not have a medical purpose.

If however, the *in vitro* examination of human specimens for the detection of biological or chemical warfare agents with a medical purpose is one of the intended uses of a specific product, the IVDD will apply.

2.6. 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 abuse/alcohol, are not qualified as IVD.

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

2.7. Relation with the Biocides Directive 98/8/EC

The products falling within the scope of the IVDD are excluded from the scope of Directive 98/8/EC. Directive 98/8/EC is currently under revision.

Part B – Classification

1. General principles on Classification

The *in vitro* diagnostic medical devices are classified into **two main product classes**:

- the large majority of devices does not constitute a direct risk to patients or public health and are used by competently trained professionals, and the results obtained can often be confirmed by other means, the conformity assessment procedures can be carried out, as a general rule, under the sole responsibility of the manufacturer being this IVD medical devices currently named as “general IVD”.

IVD intended to be used by lay persons are currently named as “self-testing IVD” and have specific requisites in the Directive regarding both the conformity evaluation procedure, with notified body intervention, and the user information essential requirements;

- the IVD for which the correct performance is essential to medical practice and the failure of which can cause a serious risk to individual patients health or public health were defined as high-risk IVD and are currently listed in annex II, list A and list B, of the Directive, and have specific requisites in the Directive regarding both the conformity evaluation procedure, with notified body intervention.

The IVD listed in Annex II list A are mainly used in blood transfusion, for the prevention of transmission of HIV and certain types of hepatitis and require a conformity assessment guaranteeing an optimum level of safety and reliability, having to fulfil the common technical specifications for their performance evaluation and re-evaluation;

According to Article 1.1 of Directive 98/79/EC, accessories shall be treated as *in vitro* diagnostic medical devices in their own right. Therefore the system of classification described in Annex II of Directive 98/79/EC applies equally to accessories.

1.1. Interpretation of Annex II, list A

1.1.1. Interpretation of “marker of infection” wording

Annex II list A of Directive 98/79/EC states that *"the lists of devices referred to in article 9(2) and (3) includesreagents, and reagents products, including calibrators and control materials for the detection, confirmation and quantification in human specimens of markers of HIV infection (HIV1 and 2), HTLV I and II, and Hepatitis B, C and D."*

It appears necessary to clarify the meaning of the word "markers of infection".

A "marker of infection" is considered as a substance that can be determined and/or be measured objectively and is an indicator of an infectious disease process. A target

marker may be a biochemical entity, genetic profile, nucleic acid, antigen, antibody, virus, bacteria or other substance.

1.1.2. Clarification of “rare” blood groups and subgroups

Annex II List A includes reagents for determining blood groups of ‘ABO system, rhesus (C, c, D, E, e) and anti-Kell’.

Questions have arisen as to the scope of devices and reagents covered and in particular so called “rare” blood groups and subgroups.

List A refers to:

“Reagents and reagent products, including related calibrators and control materials, for determining the following blood groups: ABO system, rhesus (C, c, D, E, e) anti-Kell”.

The use of the word ‘system’ appears to have led to some confusion.

The table below defines reagents and devices that are included within Annex II List A. These reagents are used for the routine determination of ABO, Rh and K types.

TABLE 1 – Reagents covered by Annex II, List A Annex II List A Terminology	Reagents & Devices Included*	Corresponding Antigen - ISBT Nomenclature
ABO System	Anti-A Anti-B Anti-AB Reagent red cells for reverse grouping	ABO1 ABO2 ABO1, ABO2 Not relevant
Rhesus (C, c, D, E, e)	Anti-D Anti-C Anti-E Anti-c Anti-e	RH1 RH2 RH3 RH4 RH5
Anti-Kell	Anti-K	K1

** Reagents and devices included:*

This column only concerns denomination of markers based on antibody/antigen assays and does not mean to exclude devices applying other technologies for the determination of ABO system, rhesus (C, c, D, E, e) anti-Kell”.

Other antigens, subgroups and variants of these systems are of minor importance in transfusion practice. Therefore, reagents for the characterization of these antigens are not included in Annex II. Blood grouping reagents/devices not listed in Annex II are regulated as general IVDs.

1.2. Interpretation of Annex II, list B

1.2.1. Classification of *Chlamydia detection IVD medical devices*

Annex II list B in the Directive refers to 'chlamydia' as a human infection.

The Directive does not differentiate between species, it simply states 'for determining the following human infections: cytomegalovirus, chlamydia':

— reagents and reagent products, including related calibrators and control materials, for determining the following human infections: cytomegalovirus, chlamydia,

Due to the chlamydia taxonomic reclassification, the former species *Chlamydia pneumoniae*, *Chlamydia pecorum* and *Chlamydia psittaci* were moved to the new genus *Chlamydophila*. The term "Chlamydia" in Annex II List B of Directive 98/79/EC should be understood as including the above mentioned species from genus *Chlamydophila* and genus *Chlamydia*.

1.2.2. Classification of *in vitro* diagnostic kits measuring parameters which can be used for evaluating the risk of trisomy 21

The manufacturer may choose to put kits intended for the measurement of parameters which can be used for evaluating the risk of trisomy 21, such as AFP, hCG, hCG-beta, estriol and PAPP-A, on the market with no intended use of risk evaluation of trisomy 21.

In that case, such kits shall clearly not be intended for the risk evaluation of trisomy 21, and shall not include information concerning the measured parameter in the risk evaluation of trisomy 21 in the instructions for use.

These kits are classified as general IVD and are to be placed on the marked following Annex III.

A consensus has been reached that in that case the insert or the packaging shall mention "this kit is NOT intended to be used for the risk evaluation of trisomy 21".

For further guidance on this subject, please consult the consensus statement "Requirements for *in vitro* diagnostic kits measuring parameters which can be used for evaluating the risk of trisomy 21" available on the European Commission website⁵.

⁵ http://ec.europa.eu/health/medical-devices/files/guide-stds-directives/trisomy_21_en.pdf