Safeguarding public health

MHRA

COMPETENT AUTHORITY (UK)

19

EC MEDICAL DEVICES DIRECTIVES

GUIDANCE NOTES ON IN VITRO DIAGNOSTIC MEDICAL DEVICES DIRECTIVE 98/79/EC

Amended February 2006

Medicines and Healthcare products Regulatory Agency

CONTENTS **PAGE**

INTRODUCTION 4

THE IN VITRO DIAGNOSITIC MEDICAL DEVICES DIRECTIVE – LEGISLATIVE STATUS 4

AIM OF THE DIRECTIVE 4

ENTRY INTO FORCE 4 - 5

SCOPE OF THE DIRECTIVE 5

WHAT IS AN IN VITRO DIAGNOSTIC MEDICAL DEVICE? 5

SPECIMEN RECEPTACLES 6

PRODUCTS FOR GENERAL LABORATORY USE 6

ACCESSORIES TO IVDS 6

DEVICES FOR PERFORMANCE EVALUATION 7

CERTIFIED REFERENCE MATERIAL 7

IVDS NOT PLACED ON THE MARKET 7

EXEMPTION FOR HEALTH INSTIUTIONS 7 - 8

TRADE FAIRS ETC 8

THE CONFORMITY ASSESSMENT PROCESS 8

OVERVIEW 8 - 9

MANUFACTURER 9

NOTIFIED BODY 9 – 10

ESSENTIAL REQUIREMENTS 10

LEVEL OF REGULATORY CONTROL 10

THE FOUR CATEGORIES 11

THE CONFORIMITY ASSESSMENT ROUTES 11

GENERAL IVDS 11

SELF-TEST IVDS NOT COVERED IN ANNEX II 11 - 12

ANNEX II IVDS 12

ANNEX II LIST B IVDS 12

CONFORMITY ASSESSMENT PROCEDURE 13 - 14

DOCUMENTATION 15
HARMONISED STANDARDS 15
COMMON TECHNICAL SPECIFICATIONS 15
THE CE MARKING 16
WHAT THE CE MARK MEANS 16
AFFIXING THE CE MARKING 16
DEVICES NOT PLACED ON THE MARKET 16 - 17
OTHER REGULATORY REQUIREMENTS 17
LANGUAGE USED IN LABELLING AND INSTRUCTIONS FOR USE 17
REGISTRATION 17 – 18
AUTHORISED REPRESENTATIVE 18
EUROPEAN DATABANK 18
TRANSITIONAL ARRANGEMENTS PENDING THE SETTING UP OF THE DATABASE 19
POST MARKET SURVEILLANCE AND VIGILANCE PROCEDURES 19
MEMBER STATES REPORTING OBLIGATIONS 19
FURTHER INFORMATION 19 - 20

INTRODUCTION

This guidance note represents the Department's current view of the law. It is intended as general guidance only and should not be regarded as an authoritative statement of the law, nor as having any legal consequence. An authoritative statement of the law can only be given by the courts. It follows that those affected by this guidance should not rely on this document but should reach their own decisions in conjunction with their lawyers and other professional advisers. The MHRA does not accept liability for any errors, omissions or misleading or other statements in this note, whether negligent or otherwise.

THE IN VITRO DIAGNOSTIC MEDICAL DEVICES DIRECTIVE - LEGISLATIVE STATUS

The *In Vitro* Diagnostic Medical Devices Directive (98/79/EC) ("the Directive") was formally adopted in October 1998 and published in the Official Journal of European Communities on 7 December 1998 (ref OJ No. L331 7.12.98 p.1). The Directive was initially implemented into UK law by the In Vitro Diagnostic Medical Devices Regulations 2000, which have now been consolidated in the Medical Devices Regulations 2002 (S.I. 2002 No. 618), as amended by the Medical Devices (Amendment) Regulations 2003 (S.I. 2003 No. 1697). References in this note to the Regulations are to the Medical Devices Regulations 2002, as amended.

AIM OF THE DIRECTIVE

The Directive introduced for the first time common regulatory requirements dealing specifically with the safety, quality and performance of *in vitro* diagnostic medical devices (IVDs), thereby bringing them into line with other medical devices. In outline, the Directive is intended to ensure that IVDs do not compromise the health and safety of patients, users and third parties and attain the performance levels attributed to them by their manufacturer.

ENTRY INTO FORCE

The relevant provisions of the Directive came into force on 7 June 2000. There was a transitional period until December 2003. From this date IVDs that are placed on the market must comply with the Directive and Regulations. Non-compliant IVDs which have been placed on the market by 7 December 2003 must

have been put into service (i.e. first made available to a final user) by 7 December 2005.

SCOPE OF THE DIRECTIVE

WHAT IS AN IN VITRO DIAGNOSTIC MEDICAL DEVICE?

The Directive (see also Regulation 2) defines an IVD as –

"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."

This definition needs to be read in conjunction with the definition of a medical device in the Directive (see also Regulation 2):

'Medical device' means any instrument, apparatus, appliance, material or other article, whether used alone or in combination, including the software necessary for its proper application, intended by the manufacturer to be used for human beings for the purpose of:

- diagnosis, prevention, monitoring, treatment or alleviation of disease,
- diagnosis, monitoring, treatment, alleviation, or compensation for an injury or handicap,
- investigation, replacement or modification of the anatomy or of a physiological process,
- control of conception,

and which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means."

SPECIMEN RECEPTACLES

"Specimen receptacles" are devices, whether vacuum-type or not, specifically intended by the manufacturer for the primary containment and preservation of specimens derived from the human body for the purpose of *in vitro* diagnostic examination. Specimen receptacles are considered to be IVDs and therefore fall within the scope of the Directive/Regulations.

PRODUCTS FOR GENERAL LABORATORY USE

Products for general laboratory use are not IVDs unless, in view of their characteristics, they are intended specifically by their manufacturer to be used for *in vitro* diagnostic examination of samples derived from the human body for the purposes outlined in the definition of an IVD.

ACCESSORIES TO IVDS

“Accessory” means “an article which, whilst not being an *in vitro* diagnostic medical device, 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.” (Article 1.2(c) and Regulation 32(1)).

For the purposes of the Directive and Regulations accessories are treated as IVDs in their own right.

However "invasive sampling devices" or those which are directly applied to the human body for the purpose of obtaining a specimen, are not considered to be accessories to IVDs. Generally, such devices will be regulated by Directive 93/42. However, where a diagnostic device incorporates an invasive element and a diagnostic element and is sold as a single integrated unit (rather than two separate products within the same pack) the MHRA view is that such a device will generally be treated as an IVD, rather than a general device regulated by Directive 93/42.

DEVICES FOR PERFORMANCE EVALUATION

A “device for performance evaluation" means a device intended by the manufacturer to be subject to one or more performance evaluation studies in laboratories for medical analyses, or in other appropriate environments outside his own premises. Instruments, apparatus, appliances, materials or other articles which are intended to be used for research purposes without any medical objective are not regarded as devices for performance evaluation.

Devices for performance evaluation are not subject to the normal conformity assessment/CE marking procedures (which are detailed below), but manufacturers must draw up the statement and follow the procedure set out in Annex VIII of the Directive and must also register with the Competent Authority (see later under “Registration” and also Guidance Notes 18 for further information).

CERTIFIED REFERENCE MATERIAL

Although internationally certified reference material and those materials used for external quality assurance schemes are not covered by the legislation, calibrators and control materials needed to establish or verify performance of devices are IVDs.

IVDs NOT PLACED ON THE MARKET

The conformity assessment procedures apply not only to IVDs which are placed on the market, but also to any person who manufactures IVDs and, without placing them on the market, “puts them into service and uses them within the context of his professional activity.” (Article 9.13 of the Directive). Thus, for example, a person who manufactures an IVD and then uses it to provide diagnostic services would generally need to comply with the appropriate conformity assessment procedure in respect of that device.

EXEMPTION FOR HEALTH INSTITUTIONS

Article 1.5 of the Directive (see Regulation 33) excludes from its scope devices “manufactured and used only within the same health institution and on the

premises of their manufacture or used on premises in the immediate vicinity without having being transferred to another legal entity."

As to the ambit of this exemption, it is clear that where a health institution manufactures an IVD and transfers it to another legal entity (whether free or as part of a commercial transaction), the exemption does not apply and therefore the Directive and Regulations do apply.

The application of the exemption is more complex in relation to health institutions which manufacture IVDs and do not place those IVDs on the market, but do put those IVDS into service and use them in the context of their professional activity. We have received a large number of queries from health institutions who have concerns about the applicability of the exemption in these circumstances.

Given the different issues which can arise in practice, we are producing specific guidance for health institutions on the application of this exemption, which will be placed on our website.

TRADE FAIRS ETC

IVDs which are not in compliance with the regulatory requirements may be shown at trade fairs, exhibitions, demonstrations, scientific or technical gatherings etc. provided that such devices are not used on specimens taken from the participants and a visible sign clearly indicates that the device cannot be marketed or put into service until it complies with the requirements of the Directive.

THE CONFORMITY ASSESSMENT PROCESS

OVERVIEW

In general terms, a manufacturer wishing to place his products on the market under this Directive must:

- assign his devices to one of the relevant risk categories defined in the Directive;
- ensure that the device meets the "essential requirements" specified in Annex I of the Directive;
- follow the appropriate conformity assessment procedure;

- if appropriate (depending on the risk category of the device), ensure that an independent certification body (called a “Notified Body”) is involved in the conformity assessment procedure.

As stated earlier, manufacturers of IVDs which are not placed on the market but which are put into service and used in the context of the manufacturer’s professional activity must also follow the appropriate conformity assessment procedure.

Definitions and further detail are provided below.

MANUFACTURER

The manufacturer is defined in the Directive (see also Regulation 2) as:

a) the “person with responsibility for the design, manufacture, packaging and labelling of a device before it is placed on the market under his own name, regardless of whether these operations are carried out by that person himself or on his behalf by a third party;” or

b) a person who “assembles, packages, processes, fully refurbishes and/or labels one or more ready made products and/or assigns to them their intended purpose as devices with a view to their being placed on the market under his own name.” This does not apply to a person who assembles or adapts devices already on the market to their intended purpose for an individual patient.

NOTIFIED BODY

A "Notified Body" is a certification organisation which the Competent Authority designates to carry out certain tasks in respect of the conformity assessment procedures described in the Annexes to the Directive. A notified body must be qualified to perform all the functions set out in any Annex for which it is designated. The tasks which a notified body can carry out may be restricted by the Competent Authority. The activities of notified bodies are regularly monitored.

Manufacturers are free to apply to any notified body in the EU designated to carry out the desired conformity assessment procedure, regardless of which Member State that notified body is designated in.

Manufacturers are required to inform their notified body of changes to their product ranges and quality system. In cases where design or type examination has been carried out by the notified body the manufacturer is required to notify them of changes to the design, as well as any information they have on changes to the pathogen and markers of infection to be tested. All such changes need to be approved by the notified body prior to implementation.

Further information on the role of notified bodies can be found in EC Directives Bulletin Number 6.

ESSENTIAL REQUIREMENTS

Annex I of the Directive lists various "essential requirements" with which IVDs must comply before being placed on the market/put into service. These aim to ensure that IVDs do not compromise the health and safety of patients, users, and others, and are designed and manufactured so that they are suitable for the relevant purpose specified by the manufacturer and achieve the performances stated by the manufacturer. Not all the essential requirements will apply to all devices and it is for the manufacturer of the device to assess which are appropriate for his particular product. In determining this, account must be taken of the intended purpose of the device.

LEVEL OF REGULATORY CONTROL

The majority of IVDs do not require the intervention of a notified body in the conformity assessment process. However, for some IVDs (the correct performance of which is perceived to be essential to health), involvement of a notified body will be required.

For the purposes of the conformity assessment procedures, the Directive groups IVDs into four categories.

THE FOUR CATEGORIES

These categories are, in order of increasing perceived risk:

- general IVDs, i.e. all IVDs other than those covered by Annex II and IVDs for self-testing;
- IVDs for self-testing (a device intended by the manufacturer to be able to be used by lay persons in a home environment) excluding self-test devices covered in Annex II;
- IVDs in Annex II List B of the Directive: Which, amongst others, includes reagents products for rubella, toxoplasmosis and phenylketonuria as well as devices for self testing for blood sugar;
- IVDs in Annex II List A of the Directive: Which includes reagents and products for HIV I and II, Hepatitis B, C and D, and reagent products for determining ABO systems and anti-kell.

THE CONFORMITY ASSESSMENT ROUTES

In order to demonstrate compliance with the essential requirements, the manufacturer must follow the conformity assessment procedure appropriate for the category of IVD concerned. Conformity assessment routes are detailed in Regulation 40 (Article 9 of the Directive), which cross-refers to the relevant Annexes. The conformity assessment routes are outlined below.

GENERAL IVDs

The manufacturer must fulfil the applicable obligations imposed by sections 1 to 5 of Annex III and must declare and ensure that the device meets the provisions of the Directive which apply. No notified body involvement is required.

SELF-TEST IVDS NOT COVERED IN ANNEX II

The manufacturer, in addition to complying with the requirements for general IVDs, must, before a declaration of conformity can be made, lodge an application

with a notified body for the examination of the design of the device (section 6 of Annex III). This will include aspects affecting its suitability for non-professional users.

Alternatively the manufacturer may follow the conformity assessment routes for higher risk products as below.

ANNEX II IVDS

For Annex II List B devices, the manufacturer must follow the applicable obligations imposed either by Annex IV, or by Annexes V and VI, or alternatively by Annexes V and VII and must declare and ensure that the device meets the provisions of the Directive which apply. For List A devices, the manufacturer must follow either Annex IV, or alternatively Annexes V and VII (i.e. it cannot follow Annexes V and VI). All Annex II IVDs require the intervention of a notified body before a declaration of conformity with the Directive can be made.

ANNEX II LIST B IVDS

The notified body will

- *either* carry out an audit of the full quality assurance system
- *or* carry out type examination plus verification of each batch or product
- *or* carry out type examination plus audit of the production quality assurance system.

A notified body will

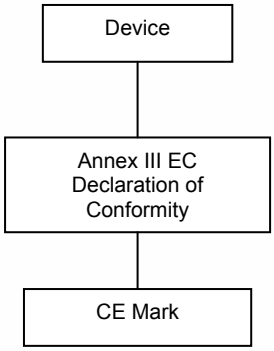
- *either* carry out an audit of the full quality assurance system and review the product design dossier
- *or* carry out type examination plus audit of the production quality assurance system.

In addition, for Annex II list A IVDs, the notified body must verify each product or batch of product before the manufacturer may place them on the market.

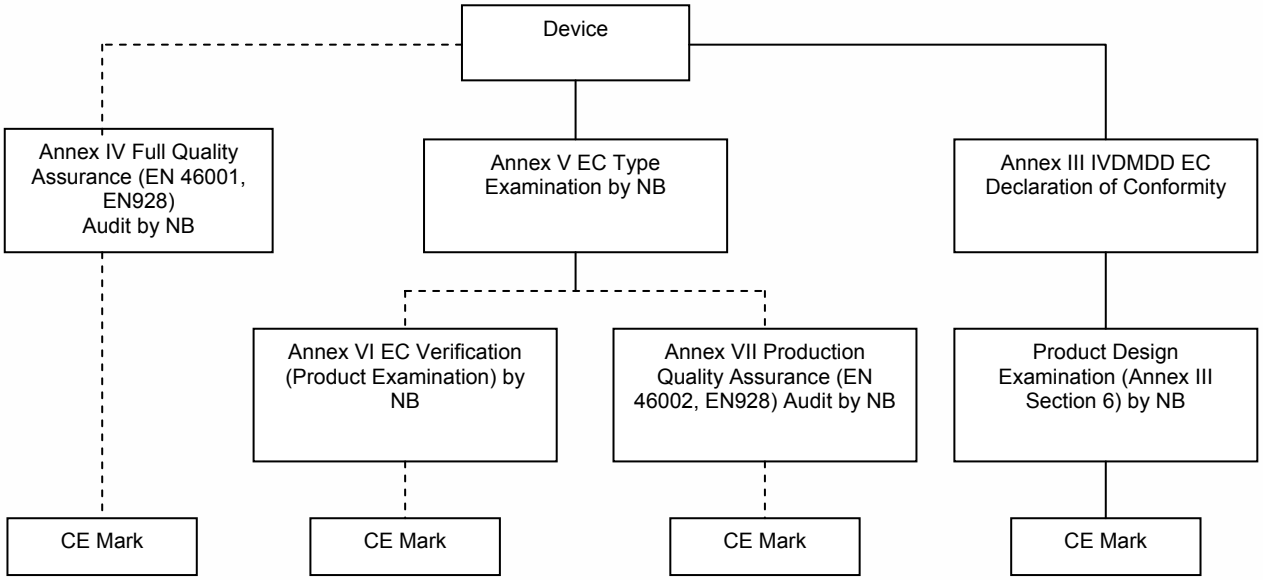
CONFORMITY ASSESSMENT PROCEDURE

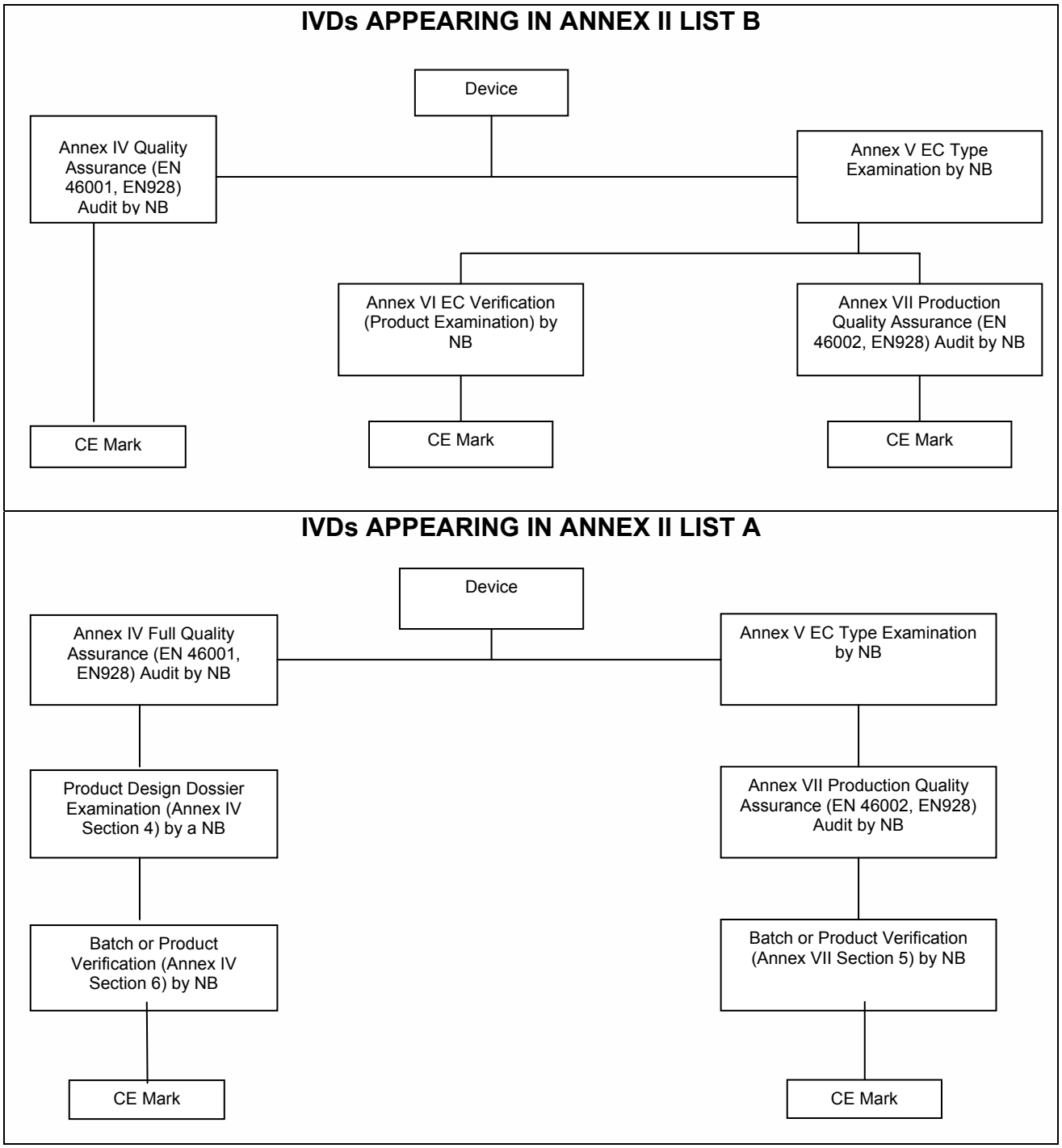
The conformity assessment routes are summarised in the attached tables.

GENERAL IVD DEVICES i.e. ALL DEVICES OTHER THAN DEVICES FOR SELF-TESTING OR DEVICES APPEARING IN ANNEX II



SELF-TESTING IVDs EXCLUDING THOSE WHICH APPEAR IN ANNEX II





It is for the manufacturer to determine how best to demonstrate conformity. The use of harmonised standards or Common Technical Specifications (see below) can be helpful.

DOCUMENTATION

The declaration of conformity, the technical documentation and the decision, reports and certificates of notified bodies must be kept available for inspection for a period of five years after manufacture of the last device.

HARMONISED STANDARDS

European Standards that have been harmonised under the IVD Directive may be used to show conformity with the relevant essential requirements. Compliance with an appropriate harmonised European Standard gives a presumption of conformity with the essential requirements to which the standard relates. The use of harmonised standards is not mandatory, and other standards exist that are not harmonised which may be used to assist in showing conformity. However, unlike harmonised standards they offer no presumption of conformity.

COMMON TECHNICAL SPECIFICATIONS

For products currently in List A of Annex II conformity assessment may involve the use of "Common Technical Specifications" (CTS) (Commission Decision of 7 May 2002 on common technical specifications for in-vitro diagnostic medical devices (notified under document C (2002) 1344) to establish performance evaluation and re-evaluation criteria, batch release criteria, reference methods and reference materials. CTS are drawn up by an Expert Group convened by the Commission rather than by the Standards Bodies. Manufacturers are expected to comply with the CTS. If they have justified reasons for not doing so they must adopt solutions that they can prove are at least equivalent to the CTS in terms of the above criteria.

As with harmonised standards, Member States must presume compliance with the essential requirements in respect of devices designed and manufactured in conformity with common technical specifications.

THE CE MARKING

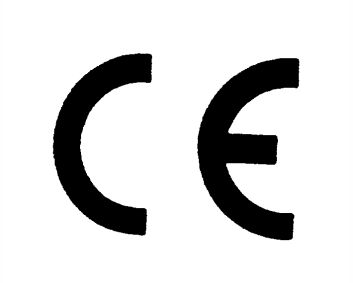
WHAT THE CE MARK MEANS

IVDs must bear the CE marking when they are placed on the market. Devices for performance evaluation do not need to be CE marked.

A manufacturer must not apply the CE mark unless he has fulfilled the applicable obligations of the Directive. The CE mark is therefore seen as a declaration by the manufacturer that the product meets all of the appropriate provisions of the relevant legislation, including those relating to safety. A device bearing a CE mark can be freely marketed anywhere in the EU without further control, except that competent authorities can take action to prevent the supply of a device in certain circumstances.

AFFIXING THE CE MARKING

The CE marking must be affixed in a visible, legible and indelible form on the device (where practicable and appropriate) and on the instructions for use. It must also appear on the sales packaging. The relevant notified body number (where one has been used) should accompany the CE marking.



DEVICES NOT PLACED ON THE MARKET

Where a device is not placed on the market, but Article 9.13 applies (i.e. the device is put into service and used in the context of a professional activity), the MHRA does not consider that it is practical or appropriate to apply a CE mark. Therefore,

we consider that the CE marking requirement in Regulation 36 does not apply to such a situation. This is in line with the approach taken in the Directive.

Further general guidance on CE marking can be found in Directives Bulletin No 2.

OTHER REGULATORY REQUIREMENTS

LANGUAGE USED IN LABELLING AND INSTRUCTIONS FOR USE

The Directive allows Member States to stipulate in their implementing legislation that the information needed to use an

IVD (labelling and instructions) is in their official language.
In the UK, Regulation 35(2) requires this information to be in English if the device may reach a final user in the UK, unless the MHRA has authorised the use of another Community language(s). If the device is a device for self-testing, the instructions for use and label must include a translation into the official language of any member state of the community in which the device reaches a final user.

REGISTRATION

Pursuant to Regulation 44, a manufacturer with a registered place of business in the UK who places a relevant device on the market (remember that for these purposes, market means Community market) or who makes available a device for performance evaluation under his own name must register with the MHRA.

In addition, a person with a registered places of business in the UK who (a) places a relevant device on the UK market, or (b) who makes a device available for performance evaluation, on behalf of a manufacturer who does not have a registered place of business in the Community or in a state which is party to an Association Agreement, must register with the MHRA (see also “Authorised Representatives” below).

Registration will not be required if the IVD was first placed on the market in another Member State (or if applicable in a state which is a party to an

Association Agreement) and the manufacturer or his authorised representative has already registered with the Competent Authorities of that state (although note the transitional arrangements which apply pending the setting up of the European database, as to which see later).

Further guidance for registration in the UK can be found in Guidance Notes Number 18.

AUTHORISED REPRESENTATIVE

Manufacturers who do not have a registered place of business in the EC (or where appropriate in a state which is party to an Association Agreement) must designate an authorised representative to perform certain obligations (e.g. to make certain documentation available on request) and may designate an authorised representative to perform other substantive obligations (see Regulation 60(1)).

Additionally, such a manufacturer must also designate an authorised representative as the person responsible for marketing the IVD in the EC and for registering that device with the appropriate Competent Authority (see Regulation 60(2)).

EUROPEAN DATABANK

A European Databank will be set up, accessible only by Member States and the European Commission. It will contain data relating to all devices available on the territory of the Community. Member States will load the information they receive from manufacturers and Notified Bodies onto the Databank.

The Databank will include;

- Data relating to registration of manufacturers and devices;
- Data relating to certificates issued, modified; complemented, suspended, withdrawn or refused by notified bodies;
- Data obtained in accordance with the vigilance system (see below).

TRANSITIONAL ARRANGEMENTS PENDING THE SETTING UP OF THE DATABASE

Until the Databank is operational, manufacturers (or their authorised representative) are required to register separately with the MHRA when they place a device on the UK market.

POST MARKET SURVEILLANCE AND VIGILANCE PROCEDURES

The conformity assessment procedures include obligations with regard to experience gained in the post-production phase, including implementation of any necessary corrective actions. Manufacturers must maintain a "vigilance system" to notify the regulatory authorities of incidents that might lead to or might have led to death or serious health consequences, or to a systematic recall of a device.

MEMBER STATES REPORTING OBLIGATIONS

In outline, Member States have obligations under the Directive, to inform the European Commission and other Member States where an IVD has been withdrawn, prohibited or restricted because it may compromise the health and safety of patients, users or others and/or where an incident has been reported as part of the vigilance procedure.

FURTHER INFORMATION

Copies of the *In Vitro* Diagnostic Medical Devices Directive (quote 98/79/EC L331/1, date of publication 7 December 1998, ISBN 0119178494), the Medical Devices Regulations 2002 (quote S.I. 2002 No. 618) and the Medical Devices (Amendment) Regulations 2003 (S.I. 2002 No 1697) are available from:

Stationery Office Books
Publications Centre
51 Nine Elms Lane

London
SW8 5DT
Tel 020 7873 9090
Fax 020 7873 8200
or accessible via www.legislation.hmso.gov.uk

Copies of guidance documents and other bulletins in our series including IVD Registration Form (RG3) can be obtained by leaving a message on: 020 7084 3203 (24 hours)

Information on medical devices published by the European Commission including copies of the Directives, further guidance (MEDDEVS), information on harmonised standards and Common Technical Specifications is available on:

http://europa.eu.int/comm/enterprise/medical_devices/index.htm

For more detailed enquiries: 020 7084 3300
Fax: 020 7084 3112
E-mail: era@mhra.gsi.gov.uk
Website: http://www.mhra .gsi.gov.uk

MHRA
Market Towers
1 Nine Elms Lane
London
SW8 5NQ

For technical enquiries:
Ring: 020 7084 3109
E-mail: dts@mhra.gsi.gov.uk