



The IVD Directive & regulations governing the sale of *in-vitro* diagnostic products in the UK

BIVDA

The British In Vitro Diagnostics Association

The difference diagnostics can make

The IVD Directive and regulations

INTRODUCTION

Prior to 1998 the UK had been, by comparison to most countries, unregulated in the area of IVDs. Sales were made by demonstrating clinical utility to purchasers who were largely laboratory professionals employed in the National Health Service.

In 1998 the European In Vitro Diagnostic Medical Devices Directive (98/79/EC) was published and subsequently transposed into UK law under the Consumer Protection Act (Medical Device Regulations 2002). Since 7th December 2003 all products placed on the market in both the European Union (EU) and the European Economic Area (EEA) have had to comply with the directive and local member state laws. In the UK, failure by a manufacturer or his authorized representative, to comply with the Medical Device Regulations is a criminal act which could, in extreme circumstances, lead to custodial sentences.

Purpose of the Directive

The purpose of the IVD directive is to facilitate a single market with minimal technical barriers to trade. It provides harmonising rules on the safety, quality and performance of IVDs, and sets out a common regulatory environment for IVDs across Europe. The Directive consists of a number of Articles which define issues such as definitions, standards and vigilance, the latter being the system by which products are monitored for performance and safety once placed on the market. These Articles are accompanied by Annexes which cover the essential requirements for products to meet, the procedures by which conformity to these requirements are shown, and classification criteria. The UK medical device regulations detail the transposition of these requirements into UK law. Any manufacturer registering in the UK must demonstrate compliance using both documents.

Competent Authorities

Government Agencies known as Competent Authorities are responsible for the requirements of the Directive being followed. Products must be registered with a Competent Authority before they can be sold in the EU. The UK Competent Authority is the Medicines and Healthcare products Regulatory Agency (MHRA), which acts on behalf of the Secretary of State for Health to ensure that IVDs do not compromise the health and safety of patients and users.

CE Mark

The CE mark is applied to the product by the manufacturer before it is placed on the European market. The CE mark may only be applied to a device for which the manufacturer has signed a declaration of conformity, indicating that it conforms to the requirements of the directive.

To affix the CE mark of conformity, the manufacturer must first decide to which category of IVDs the product belongs. It should be noted that many instruments associated with IVDs have a CE mark to show conformity to a different directive, which is concerned with electro-magnetic compatibility (EMC). The manufacturer should show clearly in his documentation which directive the CE mark refers to. Regardless of the number of directives to which a product complies there will not be more than one CE mark on a product.



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Product categories

The requirements of the directive separate IVDs into four categories which have been decided by the level of risk associated with use of the product clinically. Products considered to be of high or medium risk are detailed in Annex II lists A and B.

List A includes test kits for HIV, HTLV and Hepatitis and some blood grouping products including those used to test donated blood. List B includes, among others, test kits for rubella, PSA, toxoplasmosis and phenylketonuria, as well as self-test devices for blood glucose.

Other IVDs for self-testing other than for blood glucose also fall into a separate category. All other IVDs are in a fourth, general category as they are considered to be of low risk and for which the manufacturers can self-certify the product.

Essential requirements

The essential requirements are written in order to ensure that the products do not compromise the health and safety of patients and users, and are designed and manufactured to achieve the performance specified by the manufacturer. Not all the essential requirements will apply to all products and it is the responsibility of the manufacturer to assess which are appropriate for each product.

Conformity assessment and the role of the Notified Bodies

To demonstrate compliance with the essential requirements and affix the CE mark, the manufacturer must choose an appropriate conformity assessment route. For the general category, this is simply declaring conformity and documenting the evidence to support it. For self-test devices, in addition to this self-declaration there is a requirement for the manufacturer to submit details of the device design to an independent certification organisation known as a Notified Body. The Notified Body will assess the design of the

device in terms of its suitability for non-professional users. Alternatively manufacturers can opt to follow the routes for higher risk products. These, listed in Lists A and B of Annex II, require that the manufacturer's working practices are verified by a Notified Body. This Body will either undertake a full audit of the quality assurance system, (including design dossier review in the case of List A products), or carry out Type testing and some form of production audit or sample examination. For List A products, the manufacturer will also have to demonstrate conformity with "common technical specifications", which detail the required performance evaluation and batch release criteria.

Authorised representatives

Products which are manufactured outside of the EU must have representation within a member state. This is the designated authorized representative who is legally responsible for registering the product with a competent authority, for compliance, and subsequently post-marketing vigilance, for the product.

Use of standards

The essential requirements are underpinned by mandated standards developed by CEN (European Committee for Standardisation) with input from national standards bodies such as BSI (British Standards Institute) in the UK. These standards can assist manufacturers by providing a practical means by which conformity with the relevant essential requirements can be demonstrated. The committees arriving at these standards reflect the opinions of professional bodies, regulatory experts and industry representatives.

Vigilance

The MHRA ensures that manufacturers maintain a systematic procedure to review product performance and implement any necessary corrective actions. This requires what is known as a "vigilance system" which will notify the regulatory authorities of any incident that results, or could have resulted, in death or serious injury or to a systematic recall of a device in order to prevent the risk of these events taking place.



7 Dec 1998: Directive 98/79/EC Published	Official Journal of the European Communities (Ref.L331).
7 Dec 1999: End of transposition period	The transposition into national law by the Member States should be completed within 12 months of publication.
7 June 2000: Start of the Transition Period	<p>The first 'CE' Marking was possible.</p> <p>Member States apply the provisions of the Directive within 18 months after publication. After June 2000 and during the Transition Period, both CE- marked and non CE- marked IVD devices may be placed on the EU market (manufacturers may choose to follow either the requirements of the Directive or those of each individual Member State).</p>
7 Dec 2003: End of Transition Period	<p>Five years after the publication of the Directive. Only CE marked devices may be placed on the market.</p> <p>PLACING ON THE MARKET: "The first instance where a device, other than a device intended for performance evaluation, is made available in return for payment or free of charge, with a view to distribution and/or use on the Community market".</p>
7 Dec 2005: End of Transition for "putting into service"	<p>7 years after the publication date and end of the transition for "putting into service". Only CE-marked devices may now be put into service.</p> <p>PUTTING INTO SERVICE: "The stage at which a device has been made available to the final user as being ready for use on the Community market for the first time, for its intended purpose"</p>

Note on the Transition Period:

The purpose for the transition period (from 7th December 2003 to 7th December 2005) was to allow any non-CE marked product, **providing it was already in the supply chain prior to 7th December 2003**, to still be used.

After 7th December 2005 no product without a CE mark may be used even if it still has not reached the end of its shelf-life.

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What products are regulated by the IVD Directive?

'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.

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.'

What is the CE Mark?

The CE mark is the outward sign that a product meets all relevant new approach European directives and is therefore permitted free access to all European markets. The CE mark is not unique to diagnostic products and you will find CE marks on electrical equipment, medical devices, even toys!

What does it mean?

The CE mark means that the device meets a defined set of minimum safety requirements listed in Annex I of the IVD Directive. It also means that the device is manufactured under a quality system.

What does the CE mark look like?

The CE mark may or may not have a number next to it. The IVD Directive has a classification system and moderate, high risk and self test IVDs all require a review by an independent organisation called a Notified Body. The number beneath the CE mark identifies the Notified Body who has performed the review.



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Useful References:

1. The IVD Directive (98/79/EU)
http://europa.eu.int/smartapi/cgi/sga_doc?smartapi!celexapi!prod!CELEXnumdoc&lg=EN&numdoc=31998L0079&model=guichett
2. MHRA introduction to the IVD Directive
<http://www.medical-devices.gov.uk/mda/mdawebsitev2.nsf/webvwIndex/0B61F6FE70183A5900256AC3003AB40E?OPEN>
3. Statutory Instrument 2002 No. 618 -The Medical Devices Regulations 2002 www.jimandsteve.co.uk/new_jlcs/jlcs_html/medical.htm
4. Medicines and Healthcare products Regulatory Agency (MHRA) www.medica-devices.gov.uk
5. European Diagnostic Manufacturers Association (EDMA) www.edma-ivd.be
6. The European Commission http://europa.eu.int/comm/enterprise/medical_devices/guidelinesmed/baseguidelines.htm
7. CEN & National standardisation bodies (Europe)
www.cenorm.be/standardization/Standardization.htm
www.cenorm.be/aboutcen/whatis/membership/members.htm
8. ISO (International) www.iso.ch
9. i-bio, the UK Government Department of Trade & Industry website www.i-bio.gov.uk
10. Global Harmonisation Task Force www.ghtf.org
11. Blue Guide (Vade Mecum) www.eotc.be



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