HPRA
An tÚdarás Rialála Táirgí Sláinte
Health Products Regulatory Authority

Guide to
In-Vitro Diagnostic Medical Devices Legislation

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This guide does not purport to be an interpretation of law and/or regulations and is for guidance purposes only.

CONTENTS

1 SCOPE

The purpose of this document is to provide guidance on the regulatory control of in- vitro diagnostic medical devices on the Irish market. It sets out, inter alia, the key elements of Directive 98/79/EEC on *in-vitro* diagnostic medical devices and the related Irish Regulation S.I. No. 304 of 2001, European Communities (*In-vitro* Diagnostic Medical Devices) Regulations, 2001 hereafter referred to as the 'Directive' or the 'Regulation'.

2 INTRODUCTION

On 29 June 2001, the Minister for Health and Children appointed the Health Products Regulatory Authority (HPRA) as the Competent Authority for *in-vitro* diagnostic medical devices in Ireland. Subsequently in October 2001, the HPRA became the Competent Authority for general and active implantable medical devices in Ireland following transfer of responsibility from the Department of Health and Children. The HPRA is also the Irish regulatory body that acts as the Competent Authority (CA) for both human and veterinary medicines in Ireland.

3 LEGISLATION

In-vitro diagnostic medical devices are regulated according to the following regulations:

- *In-vitro* Diagnostic Medical Devices Directive 98/79/EC
- Commission Decision of 07/05/02 on Common Technical Specifications (CTS) for IVD Medical Devices

The former is transposed into Irish law by way of:

- S.I. No. 304 of 2001, European Communities (*In-vitro* Diagnostic Medical Devices) Regulations, 2001

The latter is a Commission Decision that does not require transposition and is effective from the date of publication.

It should also be noted that the Irish Regulation should be read in association with the Directive as the Annexes to the Directive are simply referenced in the Irish Regulation, i.e. they are not transposed. Attention should also be made to the recitals in the Directive, as answers to many important points which are raised by manufacturers are addressed in the recitals.

In Ireland, the IVD legislation took effect from 29 June 2001. A transition period was allowed to facilitate manufacturers' understanding and compliance with the legislation until 7 December 2003. It should be noted that an additional period of two years was built into the legislation to allow for devices to be 'put into service' until 7 December 2005.

There are two key definitions which must be understood with regard to the implementation of the legislation as follows:

Placing on the Market means the first making available in return for payment or free of charge of a device other than a device intended for performance evaluation with a view to distribution and/or use on the Community market, regardless of whether it is new or fully refurbished.

Putting into Service means 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.

The legislation applied from 7 December 2003 to all products placed on the market. However there was a facility built into the legislation to allow manufacturers to run down stock that had been manufactured before that date. The term 'putting into service' means that product which was in the distribution channels before 7 December 2003 could be subsequently placed on the market without a CE marking until 7 December 2005. This did not mean that manufacturers could stock pile in order to delay CE marking.

It should also be noted that based on technological advances and state of the art technologies the legislation has a built in mechanism to allow for the addition or removal of high risk IVD medical devices to the Annex II list of devices. It states in the legislation that 'Account will be taken of technological progress and developments in the field of health protection'. Consequently at any time Annex II may be amended to update or extend it once a substantiated request is provided. This process is carried out via the Regulatory Committee under Article 7 of Directive 98/79/EC. All interested parties are consulted regarding such amendments via the Medical Devices Expert Group (MDEG) and appropriate associated working groups.

4 PRODUCTS EXCLUDED FROM THE LEGISLATION

The IVD Directive makes reference to products that are specifically excluded from its scope. The following is a list of such products:

- Research only products with no medical objective (Recital 8)
- Certified reference materials and materials used for external QA schemes (Recital 9)
- Reagents that are produced in a health institution for use in that institution (Recital 10)
- Devices manufactured within the same Institution without being transferred to another legal entity (Article 1.5 of the Directive)
- Medical devices exhibited at trade fairs, exhibitions, demonstrations, scientific or technical gatherings provided no specimens are taken from patients (Article 4.3 of the Directive)

- Individual devices which may be approved in an emergency by the CA in the interest of the protection of public health (Article 9.12 of the Directive)

5 ROLE OF THE COMPETENT AUTHORITY

The HPRA will carry out the functions of the CA for medical devices as outlined in legislation as follows:

- The maintenance of a register of IVD medical device manufacturers and the medical devices that they place on the Irish market. Further details on the Registration system can be found in the HPRA 'Guide to the Registration of Persons Responsible for Placing In-vitro Diagnostic Medical Devices on the Market in Accordance with S.I. No. 304 of 2001'.

- The establishment and administration of a vigilance system for incidents attributable to medical devices (see HPRA 'Guide to the Vigilance System for Medical Devices' and the 'Guide to Field Safety Corrective Actions for Medical Devices and In-vitro Diagnostic Medical Devices').

- The examination and approval, if acceptable, of applications for performance evaluation for IVDs.

- The designation and monitoring of Notified Bodies in Ireland.

- The maintenance of market surveillance systems, which may involve the inspection of IVD manufacturers of medical devices and their authorised representatives for compliance with the legislation.

- Enforcement of the legislation where necessary.

- The participation in international activities including various relevant EU working groups and committees at the EU Commission.

- Generation of certificates of free sale for Irish based IVD manufacturers.

6 MANUFACTURER AND OWN BRAND LABELLING

Under the legislation a manufacturer is defined as the 'person who is responsible 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'. It must be noted that the definition of manufacturer also applies to 'own brand' labelling of medical devices.

To clarify this point an 'own brand labeller' is the person who places the product on the market under his own name or trademark and is therefore the manufacturer (as defined) for the purposes of the legislation. The own brand labeller may not be the person who actually designed, manufactured, packaged or labelled the product but nevertheless the regulatory responsibility rests with him alone if he is responsible for placing the product on the market. He must ensure that:

- The appropriate conformity assessment procedure is correctly followed by him and any sub-contractor involved;
- If appropriate, an application is lodged with a Notified Body;
- He makes available to the Competent Authority and the Notified Body that is involved for CE marking, appropriate documentation necessary for them to fulfil their respective responsibilities;
- He makes a Declaration of Conformity for the products concerned, and retains them for future reference by the Competent Authority;
- He registers his organisation and devices with the CA;
- The CE marking of conformity is properly applied;
- Post-marketing obligations such as vigilance are implemented.

In general, where any of the manufacturer's responsibilities are subcontracted to another party, contractual arrangement should ensure that the subcontractors meet the obligations of the legislation.

A distributor whose name appears on the packaging, labels or instructions for use is not considered to be an own brand labeller or a manufacturer if it is clear that the product is being placed on the market under the actual manufacturer's own name or that of the authorised representative.

The legislation imposes obligations on manufacturers with respect to:

- Post production monitoring, and
- the reporting of adverse incidents, and any malfunction or deterioration, which might lead to an adverse incident, to the Competent Authority.

Manufacturers, including own brand labellers, should be familiar with their legislative obligations regarding use of the CE mark. All obligations to report to the Competent Authority should be taken seriously. The consequences of not reporting incidents involving products for which there may be several own brand labellers could be particularly serious. The HPRA considers that it is the responsibility of the own brand labeller to ensure that incidents or potential incidents with a medical device that is being placed on the market under his name should also be notified to the 'actual manufacturer' of the medical device. It is also the responsibility of the actual manufacturer of the medical device, if he is aware of a particular issue with his medical devices

to ensure that own brand labellers are informed of the issue so that the appropriate corrective action can be implemented in the interest of public health.

7 CLASSIFICATION OF IVDS

As with all other medical devices, classification is based on perceived risk. IVD medical devices are categorised by risk as follows:

- Those that constitute a direct risk to patients

- Those that could constitute a serious risk to heath and are essential to control, e.g. AIDS and hepatitis, etc.

These categories are then subdivided into a further four classes dependent again on risk and the level of conformity assessment required. The following table provides a summary of the class, perceived risk and conformity assessment requirement.

For *in-vitro* diagnostic medical devices the categories are as follows:

CLASS	TYPE	CONFORMITY ASSESSMENT
General (Annex III excluding section 6)	Low Risk	Manufacturer
List B (Annex II)	Significant Risk	Notified Body at production
List A (Annex II)	Highest Risk	Notified Body at design and production and common technical specifications
Devices for Self-testing not listed in Annex II (Annex III, including Section 6)	Significant Risk	Notified Body at design and production

8 IRISH NOTIFIED BODY

Currently, one Notified Body exists for the purposes of the IVD legislation in Ireland. The National Standards Authority of Ireland (NSAI) was designated as the first Irish Notified Body for IVDs on 31 July 2002 under Article 15 of the Directive 98/79/EC and Article 11 of S.I. No. 304 of 2001 European Communities (In-vitro Diagnostic Medical Devices) Regulations, 2001.

The scope of the designation includes Annex II List A virology products, Annex II List B products and self-test medical devices.

As part of the responsibility of the HPRA in its role as Irish Competent Authority for IVDs, it undertakes regular surveillance audits of the NSAI, and its auditors are also monitored by way of observed audits. Manufacturers may from time to time therefore be informed by the Notified Body that an HPRA auditor will accompany the Notified Body audit for the purposes of surveillance of the performance of the Notified Body auditor. It should be noted however that there would be no involvement by the HPRA auditor in the audit process itself.

It should be noted that Irish manufacturers of IVDs may choose to use any Notified Body from the list of designated Notified Bodies in Europe from the Official Journal of the European Commission.

9 CONFORMITY ASSESSMENT

Conformity assessment is the process of review that takes place by the manufacturer and/or the Notified Body in order to ensure that safe and compliant product is placed on the EU market. On completion of conformity assessment the manufacturer is entitled to place the CE marking on a medical device. All IVD medical devices when placed on the market must comply with the legislation.

A declaration of conformity is required for all IVD medical devices. The responsibility for preparation rests with the manufacturer. It is the procedure whereby the manufacturer or the authorised representative ensures and declares that the products concerned meet the provisions of the legislation that apply to them. It should be noted that the declaration of conformity must be kept in the European Community at all times and be readily available for inspection by the CA.

The following is a list of key points to note:

- All IVDs must meet the Essential Requirements of Annex 1 of the Directive (Article 3 of the Directive) and the relevant annex that applies based on risk of product (Article 9 of the Directive)

- High risk Annex II list A devices require batch release by manufacturer following independent testing by the Notified Body

- A certificate of conformity has a maximum validity of five years and may be extended on application to the Notified Body (Article 9.10 of the Directive)

- Manufacturing covers both manufacture and packaging (Recital 19)

- All IVD medical devices manufactured in Ireland and which are intended to be placed on the European market must be notified for registration purposes to the HPRA (Article 10 of the Directive)

10 USE OF COMMON TECHNICAL SPECIFICATION AND STANDARDS

The Common Technical Specification (CTS) is binding legislation which must be applied to ensure that high-risk IVD medical devices listed in Annex II are in compliance with the legislative requirements. It applies specifically to all Annex II, List A devices. In the future, and if deemed necessary, it could be applied to Annex II, List B devices on justified grounds. The CTS is used to establish appropriate performance evaluation and re-evaluation, batch release criteria, reference methods and reference materials for Annex II, List A medical devices. It is used for evaluation of safety and for performance evaluation and re-evaluation of high risk IVDs (Recital 17) similar to those used for evaluation of blood transfusion transmittable disease and HIV infection.

If, for duly justified reasons the manufacturers do not comply with the CTS, they must adopt solutions of a level at least equivalent to the CTS.

Standards are used as tools which, when used, imply presumption of conformity with the legislation. They are developed by the European Committee for Standardisation (CEN) and the European Committee for Electrochemical Standardisation (CENELEC) (bodies of the European Commission) following a mandate from the Medical Devices Expert Group (MDEG). Standards in general are used to prevent and reduce the risk associated with the design, manufacturing and packaging of a device (Recital 15, 16).

Standards should be used if available in descending order:
- Harmonised standards
- National standards
- Other

If a harmonised standard is not used by a manufacturer, they must justify not using it and at least use a method which is equivalent to provide conformity with the legislation.

11 CA CONTACT WITH THE MANUFACTURER

The HPRA in its role as CA may from time to time have contact with manufacturers or their authorised representatives placing product on the Irish market. The HPRA may be in communication with the manufacturer or the authorised representative in relation to:

- Declaration of conformity and technical documentation referred to in Annex III - Annex VII as well as the decisions, reports and certificates established by the Notified Bodies. These are to

be made available on request to the CA for inspection up to five years after the last product is manufactured. (Article 9.7 of the Directive)

- Registration by manufacturers and authorised representatives (Article 10 of the Regulation)
- Request for labels and instructions for use (IFU) as part of the registration requirements. Note: it is not required to submit these at the time of registration in Ireland but they may be requested at any stage. (Article 10 of the Regulation)
- Monitoring the security and quality of devices on the market. This may require a request for supporting technical documentation or testing of the medical device, etc.
- Vigilance reports
- Reports as outlined in Article 11 of the Directive
- New products (i.e. products that are less than three years on the market) - The HPRA may request on justified grounds within 2 years of registration a report relating to the experience gained with the device subsequent to it being placed on the market
- Safety measures by use of the legislative instruments, e.g. safeguard clause, health monitoring measures
- Compliance/enforcement, e.g. wrongly affixed CE marking, etc.
- Other post-market surveillance measures

Note: the same scenarios apply to contact with other European Member States.

It should be noted that the GMDN nomenclature should be used for all communication with the HPRA. This international coding system for medical devices has been endorsed for use by the MDEG. In general the purpose of the GMDN is to have uniform recognition of terms at a global level and also in particular for post-market surveillance issues such as exchange of information between Member States for uniform implementation of the Directive and also for use in emergency protective measures. Details can be found on the GMDN website.

12 PERFORMANCE EVALUATION

All IVDs require performance evaluation in order to ensure that they achieve the performance intended (Annex 1, Article 1.3 of the Directive). The detailed procedure outlined in Annex VIII of the Directive must also be followed. Ethical issues are also addressed by reference to the Convention of Council of Europe for Protection of Human Rights and Dignity. In addition the legislation states that national Regulations of any Member State regarding ethics can also be

applied. There is no specific legislation in Ireland that needs to be applied in relation to ethical issues for medical devices evaluation or research.

Registration is required for performance evaluations under Article 10.1, 10.3, 10.5 of the Directive and Article 10.1 (b)(ii) of the Regulation. Therefore the HPRA requires notification of the intention to carry out performance evaluation by Irish-based manufacturers or their authorised representatives. While it is not specifically written into the legislation the HPRA would prefer to be notified by any manufacturer, whether based in Ireland or not, of their intention to carry out a performance evaluation study in Ireland. When Irish patient samples are used, it should be noted that devices for performance evaluation are not considered to be 'placed on the market'. While the system is a notification system with no approval granted by the HPRA, the HPRA has the obligation to monitor the security and safety of devices including those for performance evaluation (Article 2 of the Directive) placed on the Irish market.

13 RESEARCH ONLY PRODUCTS

As mentioned earlier, the use of research use only products is specifically excluded from the legislation. Recital 8 taken from the Directive should be noted in this regard as follows:

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

Therefore, research use only products to be excluded from the scope of the legislation must not have any medical objective nor be intended by the manufacturer to be used for medical purposes, i.e. they must solely be intended to be used for research purposes only. It is advisable to label such products 'for research use only' particularly in an area such as a healthcare institution to prevent such products being used for medical purposes. It should also be noted that manufacturers should not supply products labelled as 'for research use only' to the marketplace unless they are certain that there is no medical objective intended. If a medical purpose is intended the product will fall within the scope of the Directive and must comply with the legislation, i.e. it will be regarded as a device for performance evaluation.

Once a medical device is intended by the manufacturer to be used for medical purposes it must either fall under the category of a product undergoing performance evaluation for the purpose of CE marking or be a product which is CE marked. 'For research use only' products do not have an intended medical purpose. When a medical purpose has been established, based on sufficient and broadly agreed upon scientific, diagnostic and clinical evidence, then the product must comply with the requirements of the Directive before the manufacturer can place it on the market with an intended IVD use.

Further guidance is being developed at a European level and may be published at a later date.

With regard to market or feasibility studies, these cannot be considered to fall under research only product categorisation as there is a medical purpose intended. The same applies to products that are being tested against comparator products, which are considered to be IVDs.

14 LABELLING AND LEAFLETS

A label and instructions for use (IFUs) must be available with every device. Each device must be accompanied by information on how to use it safely and properly taking account of the training and knowledge of the potential user and how to identify the manufacturer. The following key points should be noted:

- Language: Member States may require the information to be supplied in their official language when the device reaches the user (Article 4.4 of the Directive)
- Harmonised symbols can be used or recognised codes or other measures (Annex 1 8.2 of the Directive)
- User type must be considered for labels and IFUs
- Instructions for use must accompany the device
- Shelf life must be stated on the packaging (Recital 20 of the Directive)
- Information must be on the device itself or on the outer packaging
- In duly justified and exceptional cases, IFUs may not be needed if the device can be used safely and properly without them

Use of electronic labelling and IFUs (Internet, CD-ROM, etc.) as such is not specifically prohibited by the IVD legislation. It should be noted that:

- The 'carrier' for IFU is not specified in the legislation
- Harmonised Standard EN 375 'General requirements for professional IFU' states 'Complete IFU may be supplied as part of the built in software of a dedicated analytical system or by electronic means…'

A guideline has been developed to advise manufacturers on how to provide IFUs and other information for the safe and effective use of IVDs while taking into account any limitations or safeguards to be employed appropriate for the user population and the media or means of supply chosen (MEDDEV 2.14/3 rev.1; IVD Guidances: Supply of Instructions For Use (IFU) and other information for *In-vitro* Diagnostic (IVD) Medical Devices). This guideline should be read in association with the labelling requirements of Annex I, Section 8 of the IVD Directive 98/79/EC and with the language requirements of the transpositions of Article 4(4) of the IVD Directive 98/79/EC by the Member States.

15 WHO TO CONTACT AT THE HPRA

This guide and associated documents can be found under the 'Publications and Forms' section of www.hpra.ie.

Alternatively, they can be obtained from the HPRA directly as follows:

Medical Devices Department
Health Products Regulatory Authority
Kevin O'Malley House
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D02 XP77

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The HPRA encourages communication with the medical device sector. Should you have specific queries please address them to the Medical Devices Department of the HPRA which will endeavour to be of assistance.

Communication can be made by telephone, fax, email or by post to the above address.