HPRA
An tÚdarás Rialála Táirgí Sláinte
Health Products Regulatory Authority

Guide for
Manufacturers of General Class *In-Vitro* Diagnostic Medical Devices

SUR-G0008-1
11 MAY 2009
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 to enable manufacturers of the general category of *in-vitro* diagnostic medical devices (IVDs) to meet the legislative requirements of S.I. No. 304 of 2001 European Communities (*In-vitro* Diagnostic Medical Devices) Regulations, 1994 which will hereafter be called the 'Regulations', and Directive 98/79/EC of the European Parliament and of the Council of 27 October 1998 on *in-vitro* diagnostic medical devices, which will hereafter be called the 'Directive'.

This document applies to all products that fall within the general category of *in-vitro* diagnostic medical devices. IVDs that fall into Annex II Lists A and B, self-testing IVDs, active implantable medical devices and general medical devices are outside the scope of this guidance. The requirements for post-market vigilance or adverse event reporting are also outside the scope of this guidance.

In using this guide, reference should be made to the HPRA 'Guide to the *in-vitro* diagnostic (IVD) medical devices legislation' and to 'Guidance Note 6: Glossary of terms for medical devices'.

2 INTRODUCTION

The Health Products Regulatory Authority (HPRA) became the Competent Authority for *in-vitro* diagnostic medical devices on 29 June 2001. The Department of Health and Children previously held this role. The Competent Authority is the body, which has the authority to act on behalf of the government of a Member State to ensure that the requirements of the Medical Devices Directives are carried out in that particular Member State. The directives and consequent national regulations determine the role of the Competent Authority, which is to ensure that all medical devices sold on the Irish market meet the essential requirements of the legislation and in doing so do not compromise the health and safety of patients, users, and where appropriate, any other persons.

3 LEGISLATION

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

- S.I. No. 304 of 2001, European Communities (In-vitro Diagnostic Medical Devices) Regulations, 2001 which transposed Directive 98/79/EC into Irish law and became mandatory on 29 June 2001

- Commission Decision of 7 May 2002 on Common Technical Specifications (CTS) for IVD Medical Devices

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

These documents are available from the Government Publications Sale Office at Molesworth Street, Dublin 2.

The Irish Regulation should be read in association with the Directive as the annexes to the Directive are only 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, until 7 December 2003, was allowed to facilitate manufacturers understanding and compliance with the legislation. It should be noted that an additional period of two years, until 7 December 2005, was built into the legislation to allow for devices to be 'put into service'.

4 DEFINITIONS

All relevant definitions may be found in *Guidance Note 6: Glossary of Terms for Medical Devices* which is available from the Human Products Safety Monitoring Department of the HPRA or can be downloaded from our website.

Particular reference should be made to:

Authorised Representative - Any natural or legal person established in the Community who explicitly designated by the manufacturer, acts and may be addressed by authorities and bodies in the European Community instead of the manufacturer with regard to the latter's obligations under the directive.

Conformity assessment - The process of demonstrating whether specified requirements relating to a product, process, service, system, person or body have been fulfilled.

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.

Manufacturer - The natural or legal 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. The obligations of the medical device directives to be met by manufacturers also apply to the natural or legal 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 a device with a view to their being placed on the market under his own name. This sub-paragraph does not apply to the person who, while not a manufacturer within the meaning of the first sub-paragraph, assembles or adapts devices already on the market to their intended purpose for an individual patient.

Risk - Combination of the probability of occurrence of harm and the severity of that harm

Risk Analysis - Systematic use of available information to identify hazards and to estimate the risk.

Technical file / Technical documentation - Set of documentation prepared by the manufacturer and made available to the Competent Authority to assess compliance with the requirements of the directive.

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.

5 GENERAL CATEGORY OF IVDS

IVDs are classified into four categories as follows:

- General IVDs (devices not listed in Annex II and not intended for self-testing)
- IVDs for self-testing (excluding self-test devices covered in Annex II)
- IVDs in Annex II List B of the Directive
- IVDs in Annex II List A of the Directive

They are classified according to the risk associated with the relative dangers to the public and/or patient treatment by an IVD failing to perform as intended. IVDs that fall into the general class are devices that are considered low risk. The vast majority of IVDs fall into this category.
Reference should be made to the *HPRA 'Guide to the in-vitro* diagnostic medical devices Legislation' for further information on the classification of IVDs, and on products that are excluded from the scope of the Regulations and the Directive.

6 REGISTRATION

Regulation 10 of the 'Regulations' and Article 10 of the Directive requires manufacturers or their authorised representatives or others placing medical devices(s) on the Community market, to provide certain information to the CA in the Member State where they have a registered place of business.

Manufacturers who have a registered place of business in Ireland and who manufacture general IVDs that are placed on the market under their own name must inform the HPRA of:

- their registered address
- information relating to the reagents, reagent products and calibration and control materials in terms of common technological characteristics and/or analytes and of any significant change thereto including discontinuation of placing on the market.

Further information regarding the registration of IVDs can be found in the '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'.

7 CE MARKING

All IVDs, with the exception of devices for performance evaluation, placed on the market must bear the CE marking (affixed following the procedure outlined in point 8 below).

Regulation 6 of the 'Regulations', and Article 16 of the Directive, state that the CE marking must be in a visible, legible and indelible form on:

- the device where practicable and appropriate, and
- on the instructions for use, and
- any sales packaging.

Manufacturers of the general class of IVDs self declare that they are in compliance with the Regulations. Therefore, it must be pointed out that such IVDs bear the CE mark without a Notified Body identification number as Notified Body intervention is not required.

8 PROCEDURE FOR AFFIXING A CE MARK FOR GENERAL IVDS

There are two key annexes in the Directive that apply to the general category of IVDs. They are:

- Annex I: Essential Requirements
- Annex III: EC Declaration of Conformity.

Below is an outline of the requirements in these schedules.

8.1 Annex I: Essential Requirements

Regulation 5 of the 'Regulations' and Article 3 of the Directive state that, "all devices must meet the Essential Requirements set out in Annex I of the Directive, which apply to them, taking account of the intended purpose of the devices concerned".

To meet the essential requirements, the manufacturer must consider:

- Safety and performance (analytical/diagnostic sensitivity, specificity, accuracy, repeatability, reproducibility…)
- Chemical, physical properties
- Infection and microbial contamination
- Manufacturing & environmental properties
- Protection against radiation, electrical risks, mechanical & thermal risks
- Requirements for devices for self-testing
- Information to be supplied by the manufacturer

It is necessary for the manufacturer of the device to review all of the essential requirements outlined in Annex 1 of the Directive against his procedures. The manufacturer must also review the essential requirements regarding the information that is to be supplied with the device, i.e. the instructions for use (IFU), and determine what is appropriate for his products.

Appendix 2 of this guide has an essential requirements checklist for the general class of IVDs, which could be used by manufacturers to assist them in satisfying their compliance with the legislation.

A device shall be treated as complying with an essential requirement if, in respect of that requirement, the device complies with a relevant harmonised/national standard, unless there are reasonable indications that the device does not comply with that requirement.

8.2 Annex III: EC Declaration of Conformity

The EC declaration of conformity is the procedure whereby the manufacturer or his authorised representative (established in the Community) who fulfils the obligations imposed

by Section 2 to 5 of Annex III (see below; technical documentation) ensures and declares that the products concerned meet the provisions of the Directive that apply to them.

8.3 Technical Documentation

According to Regulation 7(1) of the 'Regulations', a device falling within the general category of IVDs may bear the CE marking only if the manufacturer follows the EC Declaration of Conformity procedure set out in Annex III of the Directive. The requirements in relation to the technical documentation to support the devices are outlined in sections 2 to 5 of Annex III.

The manufacturer must prepare the technical documentation described below. As per Regulation 8(4) of the 'Regulations' the manufacturer must make this documentation, including the declaration of conformity, available to the HPRA for inspection purposes for a period of at least five years after the last product has been manufactured. This includes the manufacturer making the file available to his authorised representative. It also includes having the file available at the premises of the first importer into Europe if there is no designated authorised representative in the European Community.

In Ireland, the technical documentation shall be in English, as required by Regulation 8(10) of the 'Regulations'.

The technical documentation must be presented in such a manner as to allow assessment of the conformity of the products with the requirements of the Directive. This documentation must include in particular:

8.3.1 Description:

- "a general description of the product, including any variants planned"

The manufacturer should provide a general description of the product, for example; names, model number, constituents of assay kit, concentration, sizes, intended use, indications for use, contraindications.

8.3.2 Design:

- "design information, including the determination of the characteristics of the basic materials, characteristics and limitation of the performances of the devices, methods of manufacture and, in the case of instruments, design drawings, diagrams of components, sub-assemblies, circuits, etc."

The manufacturer should describe how the device has been designed, manufactured and how it should perform. Specifications including, as applicable, appropriate drawings and/or master patterns, circuits, formulation, manufacturing methods, process validation data and any

quality control procedures for the raw materials/components, intermediate products/sub-assemblies and final product should be demonstrated here. If applicable, the manufacturer should describe the constituents of their assay kit and assembly process and detail the assay reaction.

8.3.3 Design explanation:

- "the descriptions and explanations necessary to understand the above mentioned characteristics, drawings and diagrams and the operation of the product"

8.3.4 Design verification:

- "the results of the design calculations and of the inspections carried out etc."
- "the test reports"

The manufacturer may provide the results of qualification tests and design calculations relevant to the intended use of the product, including connections to other devices in order for it to operate as intended. Quality control reports and R & D reports may also be provided, such as clinical and scientific data from in-house or reference methods. Information showing that a safe design has been established for a number of years and the product has been performing as intended during that time may satisfy this requirement.

8.3.5 Quality system documentation:

- "the documentation of the quality system"

Quality system documentation includes; for example, the quality manual, the standard operating procedures and the quality records. The records must be kept updated and the people responsible for the procedures must be indicated. Also see point 8.3.13 below.

8.3.6 Combined devices:

- "if the device is to be combined with other device(s) in order to operate as intended, proof must be provided that it conforms to the essential requirements when combined with any such device(s) having the characteristics specified by the manufacturer."

Evidence must be provided that the device maintains the characteristics and meets the applicable essential requirements specified by the manufacturer when used in combination with other devices.

8.3.7 Tissues of human origin:

- "in the case of devices containing tissues of human origin or substances derived from such tissue, information on the origin of such material and on the conditions in which it was collected."

Manufacturers must document both the origin of the tissue and the conditions under which it was collected. Records of donor tested material from defined sources must be kept.

8.3.8 Risk analysis:

- "the results of the risk analysis and, where appropriate, a list of the standards referred to in Article 5, applied in full or in part, and descriptions of the solutions adopted to meet the essential requirements of the Directive if the standards referred to in Article 5 have not been applied in full."

The results of the risk analysis should be used to determine whether the risks associated with the use of the product (according to its intended use) are acceptable when evaluated against the benefits of the device to the user. This risk analysis should be based upon international or other recognized standards, and be appropriate to the complexity and risk class of the device. EN 1441 (Medical devices - risk analysis) was the harmonised standard used for this purpose. It should be noted that this standard was superseded on the 1st April 2004 by EN ISO 14971 (Medical devices - Application of risk management to medical devices).

The manufacturer should identify any potential risk that may be associated with the use of the device and should then demonstrate how that risk has been eliminated or reduced as far as possible. Market surveillance may be used as supported evidence, where applicable, to demonstrate that a device is safe or a specific risk has been adequately addressed.

This may be as simple as a one page document or it may require a complex statement including supporting scientific data depending on the type of product and its novelty and/or uniqueness.

8.3.9 Sterility:

- "in the case of sterile products or products with a special microbiological state or state of cleanliness, a description of the procedures used."

With regard to IVDs that claim to be sterile or claim to have a special microbiological state or state of cleanliness, the procedures used must be documented.

8.3.10 Performance evaluation data

- "adequate performance evaluation data showing the performances claimed by the manufacturer and supported by a reference measurement system (when available), with information on the reference methods, the reference materials, the known reference values, the accuracy and measurement units used; such data should originate from studies in a clinical or other appropriate environment or result from relevant biological references."

As per Article 1 (e) of the Directive, a device for performance evaluation means "any 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."

The definition of 'Performance Evaluation' as per EN 13612:2002, the European standard on performance evaluation is "an investigation of the performance of an *in-vitro* diagnostic medical device based upon data already available, scientific literature and/or performance evaluation studies."

Any performances stated by the manufacturer must be supported by either external performance evaluation data generated at the time of the design of the device, data established in the manufacturer's own premises during the R & D phase or by data taken from published literature. Data based on experience gained in the post-production phase may be used to support the claims made by the manufacturer.

8.3.11 Labelling:

- "the labels and instructions for use"

A label and instructions for use (IFU) must be available with every device. Each device must be accompanied by information to use it safely and properly taking account of the training and knowledge of the potential user and to identify the manufacturer. In duly justified and exceptional cases no such instructions for use are needed for a device if it can be used properly and safely without them. The labelling requirements are outlined in section 8 of the essential requirements in Annex I of the Directive. Further information on the labelling of IVDs is also provided in the HPRA *Guide to the In-vitro Diagnostic Medical Devices Legislation*.

8.3.12 Stability:

- "the results of stability studies"

Tests may be performed under ideal, real-time, shipping and storage conditions. Results from real-time and accelerated testing may be used to support the shelf life of the IVD. If an IVD is

to be refrigerated, particular care should be taken when carrying out transport studies under such conditions.

8.3.13 Quality assurance:

- "the organisational structure and responsibilities"
- "the manufacturing processes and systemic quality control of production"
- "the means to monitor the performance of the quality system"

8.3.14 Post-market surveillance procedures;

These would include vigilance, recall and field safety corrective action procedures. Refer to Point 9 below.

9 MANUFACTURER'S OBLIGATIONS

The manufacturer shall put in place and keep updated a procedure to review experience gained from devices on the market and to implement necessary corrective action, taking account of the nature and risks in relation to the product.

The Directive requires the manufacturer or his authorised representative to immediately notify the Competent Authority in Ireland, namely the HPRA, of the following incidents on learning of them:

a any malfunction of, or deterioration in, the characteristics and/or performance of a device, as well as any inadequacy in the labelling or in the instructions for use, which directly or indirectly, might lead to or might have lead to the death of a patient or user or other persons, or to a serious deterioration in his or their state of health.

b any technical or medical reason connected with the characteristics or the performance of a device for the reasons referred to in subparagraph (a) leading to a systematic recall of devices of the same type by the manufacture.

Please refer to the HPRA 'Guide to the vigilance system for medical devices' and 'Guide to field safety corrective actions for medical devices and *in-vitro* diagnostic medical device's for further information.

10 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:

Human Products Safety Monitoring Department
Health Products Regulatory Authority
Earlsfort Centre
Earlsfort Terrace
Dublin 2

Telephone: +353-1-6764971
Fax: +353-1-6767836
Email: devices@hpra.ie

The HPRA encourages communication with the medical device sector. Should you have specific queries please address them to the Human Products Safety Monitoring Department of the HPRA who will endeavour to be of assistance.

Communication can be made by telephone, fax, e-mail or by post to the above address.

APPENDIX 1 CHECKLIST FOR MANUFACTURERS OF IVDS

ITEM	YES	NO	COMMENT / REFERENCE	S.I. 304 OF 2001	DIRECTIVE 98/79/ EC
Review of definitions to confirm device is an IVD and falls into the general category.			Confirm product is an *in-vitro* diagnostic medical device and falls into the general category.	Article 2	Article 1 Annex II
Essential Requirements are met			Appendix 2 of this guide for details.	Article 5	Article 3 Annex I
Technical Documentation: - Description				Article 7	Annex III
- Design					Annex III
- Specifications			- Raw material /component - Intermediate product/sub-assembly - Final product		Annex III
- Manufacturing records			Compliance with defined procedures must be shown		Annex III
- Test records			EN 13975		Annex III
- Sterilisation records (if applicable)			EN 550 series		Annex III
- Risk analysis			EN ISO 14971		Annex III
- Stability studies			EN 13640		Annex III
- List of harmonised standards that have been applied			Products manufactured according to harmonised standards benefit of a presumption of conformity to the essential requirements		Annex I Annex III

ITEM	YES	NO	COMMENT / REFERENCE	S.I. 304 OF 2001	DIRECTIVE 98/79/ EC
- Performance evaluation			EN 13612		Annex III
- Packaging & label			EN 980		Annex I
- Instructions for use			Must be adequate and include all aspects involved in use.		Annex I Annex III
EC Declaration of Conformity					Annex III
CE mark affixed to: - Device				Article 6	Article 16 Annex X
- Instructions for use				Article 6	Article 16 Annex X Annex I
- Sales packaging				Article 6	
Quality system records			EN 13485		Annex III
Post-market surveillance records(e.g. corrective action, vigilance, recall)			Documentation must be kept available for inspection by the CA.		Annex III
Registration of manufacturer/ Authorised Representative with Competent Authority			Reference: Guide to the Registration of persons responsible for placing *in-vitro* Diagnostic Medical Devices on the Market	Article 10	Article 10

* Reference to Manufacturer's appropriate supporting documentation should be made

** This is not a comprehensive list of references and should only be used as a guide.

APPENDIX 2 ESSENTIAL REQUIREMENTS CHECKLIST FOR MANUFACTURERS OF THE GENERAL CLASS OF IVDS

ESSENTIAL PRINCIPLE	APPLICABLE TO THE DEVICE	METHOD OF CONFORMITY	IDENTITY OF SPECIFIC DOCUMENTS	GUIDANCE FOR THE MANUFACTURER OF THE DEVICE	RELEVANT HARMONISED STANDARDS
A. GENERAL REQUIREMENTS					
1. The devices must be designed and manufactured in such a way that, when used under the conditions and for the purposes intended, they will not compromise the clinical condition or the safety of patients, or the safety and health of users or, where applicable, other persons, provided that any risks which may be associated with their use constitute acceptable risks when weighed against the benefits to the patient and are compatible with a high level of protection of health and safety.				This requirement requires the device to be safe when used as intended by the manufacturer. A risk assessment according to the relevant harmonised standard should be performed.	EN ISO 14971 (Medical devices - Application of risk management to medical devices)
2. The solutions adopted by the manufacturer for the design and construction of the devices must conform to safety principles, taking account of the generally acknowledged state of the art.				To comply with this requirement, manufacturers should: review the design brief of the product review the risk analysis review published literature and experience	

ESSENTIAL PRINCIPLE	APPLICABLE TO THE DEVICE	METHOD OF CONFORMITY	IDENTITY OF SPECIFIC DOCUMENTS	GUIDANCE FOR THE MANUFACTURER OF THE DEVICE	RELEVANT HARMONISED STANDARDS
In selecting the most appropriate solutions, the manufacturer must apply the following principles in the following order: eliminate or reduce risks as far as possible (inherently safe design and construction), where appropriate take adequate protection measures including alarms if necessary, in relation to risks that cannot be eliminated, inform users of the residual risks due to any shortcomings of the protection measures adopted.				of similar devices review the packaging of the device to harmonised standards. review the labelling and instructions for use(if applicable) review final release procedures review clinical and scientific data obtained with reference methods review all safety aspects and detail any remaining risk with the final product and provide appropriate warning indications (e.g. potentially infectious materials)	
3. The devices must be designed and manufactured in such a way that they are suitable for the purposes referred to in Article 1 (2) (b), as specified by the manufacturer, taking account of the generally acknowledged state of the art. They must achieve the performances, in particular, where appropriate, in terms of analytical sensitivity, diagnostic sensitivity,				The manufacturer must have evidence that the device complies with his specified performance requirements. A design validation and test regime should reflect this. Any performances stated by the manufacturer must be supported by either external performance evaluation data generated at the time of the design of the	EN 13612:2002 (Performance evaluation of *in-vitro* diagnostic medical devices) EN ISO 17511:2003 (*In-vitro* diagnostic medical devices - Measurement of quantities in

ESSENTIAL PRINCIPLE	APPLICABLE TO THE DEVICE	METHOD OF CONFORMITY	IDENTITY OF SPECIFIC DOCUMENTS	GUIDANCE FOR THE MANUFACTURER OF THE DEVICE	RELEVANT HARMONISED STANDARDS
analytical specificity, diagnostic specificity, accuracy, repeatability, reproducibility including control of known relevant interference, and limits of detection, stated by the manufacturer. The traceability of values assigned to calibrators and/or control materials must be assured through available reference measurement procedures and/or available reference materials of a higher order.				device, data established in the manufacturer's own premises during the R&D phase or by data taken from literature. Data based on experience gained in the post-production phase may be used to support the claims made by the manufacturer. Traceability of values must be assured.	biological samples - Metrological traceability of values assigned to calibrators and control materials.)
4. The characteristics and performances referred to in sections 1 and 3 must not be adversely affected to such a degree that the health or the safety of the patient or the user and, where applicable, of other persons, are compromised during the lifetime of the device, as indicated by the manufacturer, when the device is subject to the stresses which can occur during normal conditions of use. When no lifetime is stated, the same				It should be demonstrated that the stresses that occur during the normal conditions of use intended by the manufacturer during the expected lifetime of the device are identified. Possible adverse effects must be considered and assessed. Assessments are normally done by appropriate bench testing, simulated shelf life testing and clinical evaluation if applicable.	EN13640:2002 (Stability testing of *in-vitro* diagnostic medical devices)

ESSENTIAL PRINCIPLE	APPLICABLE TO THE DEVICE	METHOD OF CONFORMITY	IDENTITY OF SPECIFIC DOCUMENTS	GUIDANCE FOR THE MANUFACTURER OF THE DEVICE	RELEVANT HARMONISED STANDARDS
applies for the lifetime reasonably to be expected of a device of that kind, having regard to the intended purpose and the anticipated use of the device.				If accessible, a review of complaints history should be used for established products. When no lifetime is stated, the lifetime will be as long as can reasonably be expected.	
5. The devices must be designed, manufactured and packed in such a way that their characteristics and performances during their intended use will not be adversely affected during transport and storage taking account of the instructions and information provided by the manufacturer.				It should be demonstrated that the stresses that can occur during the transport and storage of the device, in accordance with the instructions and information, are identified and have been addressed in the design, manufacturing, performance and packaging of the device. If accessible, a review of complaints history should be used for established products.	
B. DESIGN AND MANUFACTURING REQUIREMENTS					
1. Chemical and Physical Properties					EN 10993 series (Biological evaluation of medical devices)
1.1. The devices must be designed and manufactured in such a way as to achieve the characteristics and performances				It should be demonstrated that the materials chosen are appropriate given the intended use of the device. The types of	EN 10993 (Parts 8, 14, 15)

ESSENTIAL PRINCIPLE	APPLICABLE TO THE DEVICE	METHOD OF CONFORMITY	IDENTITY OF SPECIFIC DOCUMENTS	GUIDANCE FOR THE MANUFACTURER OF THE DEVICE	RELEVANT HARMONISED STANDARDS
referred to in Section A above on the 'General Requirements'. Particular attention must be paid to the possibility of impairment of analytical performance due to incompatibility between the materials used and the specimens (such as biological tissues, cells, body fluids and micro-organisms) intended to be used with the device, taking account of its intended purpose.				tests performed should be included in the risk analysis. A biological safety evaluation should be made in accordance with relevant harmonised standards. Historic data on materials used in similar products should also be reviewed. The combination of the constituents of the product should be reviewed in relation to interferences/incompatibility between materials used and testing substances.	
1.2. The devices must be designed, manufactured and packed in such a way as to reduce as far as possible the risk posed by product leakage, contaminants and residues to the persons involved in the transport, storage and use of the devices, taking account of the intended purpose of the products.				Any contaminants and residues in or on the device that could cause significant adverse effects should be identified and potential risks to patients or others exposed to the product should be considered and reduced as far as practicable. Leaking includes leaching. Simulated use testing should be carried out. Assessment is normally carried out by appropriate bench testing.	

ESSENTIAL PRINCIPLE	APPLICABLE TO THE DEVICE	METHOD OF CONFORMITY	IDENTITY OF SPECIFIC DOCUMENTS	GUIDANCE FOR THE MANUFACTURER OF THE DEVICE	RELEVANT HARMONISED STANDARDS
2. Infection and microbial contamination					
2.1 The devices and their manufacturing process must be designed in such a way as to eliminate or reduce as far as possible the risk of infection to the user or other persons. The design must allow easy handling and, where necessary, reduce as far as possible contamination of and leakage from the device during use and, in the case of specimen receptacles, the risk of contamination of the specimen. The manufacturing processes must be appropriate for these purposes.				Any contaminants and residues in or on the device that could cause significant adverse effects should be identified and potential risks to patients or others exposed to the product should be considered and reduced as far as practicable. Leaking includes leaching. Simulated use testing should be carried out. Assessment is normally carried out by appropriate bench testing.	EN 13641:2002 (Elimination or reduction of risk of infection related to *in-vitro* diagnostic reagents)
2.2. Where a device incorporates biological substances, the risks of infection must be reduced as far as possible by selecting appropriate donors and appropriate substances and by using appropriate, validated inactivation,				Substances of biological origin should be qualified. Where appropriate, certificates of origin from suppliers of materials of animal origin that could be associated with a substantial degree of risk of infection or	EN 12286:1998 & EN 12287:1999 (*In-vitro* diagnostic medical devices - Measurement of quantities in samples of biological origin)

ESSENTIAL PRINCIPLE	APPLICABLE TO THE DEVICE	METHOD OF CONFORMITY	IDENTITY OF SPECIFIC DOCUMENTS	GUIDANCE FOR THE MANUFACTURER OF THE DEVICE	RELEVANT HARMONISED STANDARDS
conservation, test and control procedures.				adverse reaction should be requested. Handling and processing procedures should be reviewed in relation to these materials.	
2.3 Devices labelled either as 'STERILE' or as having a special microbiological state must be designed, manufactured and packed in an appropriate pack, according to procedures suitable for ensuring that they remain in the appropriate microbiological state indicated on the label when placed on the market, under the storage and transport conditions specified by the manufacturer, until the protective packaging is damaged or opened.				IVDs that claim to be sterile, or claim to have a special microbiological state or state of cleanliness must be manufactured and packaged in a way that will not compromise the label claim of sterility.	EN 550 series
2.4 Devices labelled as 'STERILE' or as having a special microbiological state must have been processed by an appropriate, validated method.					EN 552:1994 (Sterilisation of medical devices - validation and routine control o sterilisation by irradiation)

ESSENTIAL PRINCIPLE	APPLICABLE TO THE DEVICE	METHOD OF CONFORMITY	IDENTITY OF SPECIFIC DOCUMENTS	GUIDANCE FOR THE MANUFACTURER OF THE DEVICE	RELEVANT HARMONISED STANDARDS
					EN 556-1:2001: (Sterilisation of medical devices - Requirements for medical devices to be designated 'Sterile')
2.5 Packaging systems for devices other than those referred to in section 2.3 must keep the product without deterioration at the level of cleanliness indicated by the manufacturer and, if the devices are to be sterilized prior to use reduce as far as possible the risk of microbial contamination. Steps must be taken to reduce as far as possible microbial contamination during selection and handling of raw materials, manufacture, storage and distribution where the performance of the device can be adversely affected by such contamination.					
2.6 Devices intended to be sterilized must					EN 552:1994

ESSENTIAL PRINCIPLE	APPLICABLE TO THE DEVICE	METHOD OF CONFORMITY	IDENTITY OF SPECIFIC DOCUMENTS	GUIDANCE FOR THE MANUFACTURER OF THE DEVICE	RELEVANT HARMONISED STANDARDS
be manufactured in appropriately controlled (e.g. environmental) conditions.					(Sterilisation of medical devices - validation and routine control of sterilisation by irradiation)
2.7 Packaging systems for non-sterile devices must keep the product without deterioration at the level of cleanliness stipulated and, if the devices are to be sterilized prior to use, minimize the risk of microbial contamination; the packing system must be suitable taking account of the method of sterilization indicated by the manufacturer.					
3. Manufacturing and environmental properties					
3.1 If the device is intended for use in combination with other devices or equipment, the whole combination, including the connection system must be safe and must not impair the specified				If the device is intended to be used in combination with other devices, it must maintain the characteristics and meet the applicable essential requirements specified by the manufacturer when used in	

ESSENTIAL PRINCIPLE	APPLICABLE TO THE DEVICE	METHOD OF CONFORMITY	IDENTITY OF SPECIFIC DOCUMENTS	GUIDANCE FOR THE MANUFACTURER OF THE DEVICE	RELEVANT HARMONISED STANDARDS
performances of the devices. Any restrictions on use must be indicated on the label and/or in the instructions for use.				combination with other devices. Simulated use of the performance of the combination should be carried out.	
3.2 Devices must be designed and manufactured in such a way as to reduce as far as possible the risks linked to their use in conjunction with materials, substances and gases with which they may come into contact during normal conditions of use.				Interactions with materials, substances and gases in normal use must be tested. Assessments are normally done by appropriate bench testing.	
3.3 Devices must be designed and manufactured in such a way as to remove or reduce as far as possible: the risk of injury linked to their physical features (in particular aspects of volume x pressure, dimension and, where appropriate, ergonomic features); risks linked to reasonably foreseeable external influences, such as magnetic fields, external electrical effects, electrostatic discharge, pressure,					EN 61010-2-101:2002 (Safety requirements for electrical equipment for measurement, control, and laboratory use – Part 2-101: Particular requirements for *in-vitro* diagnostic medical equipment)

ESSENTIAL PRINCIPLE	APPLICABLE TO THE DEVICE	METHOD OF CONFORMITY	IDENTITY OF SPECIFIC DOCUMENTS	GUIDANCE FOR THE MANUFACTURER OF THE DEVICE	RELEVANT HARMONISED STANDARDS
humidity, temperature or variations in pressure or acceleration or accidental penetration of substances into the device. Devices must be designed and manufactured in such a way as to provide an adequate level of intrinsic immunity of electromagnetic disturbance to enable them to operate as intended.					
3.4 Devices must be designed and manufactured in such a way as to reduce as far as possible the risks of fire or explosion during normal use in single fault condition. Particular attention must be paid to devices whose intended use includes exposure to or use in association with flammable substances or substances which could cause combustion.					EN 61010-2-101:2002 (Safety requirements for electrical equipment for measurement, control, and laboratory use - Part 2-101: Particular requirements for *in-vitro* diagnostic medical equipment)
3.5 Devices must be designed and manufactured in such a way as to facilitate the management of safe waste disposal.					
3.6 The measuring, monitoring or display					

ESSENTIAL PRINCIPLE	APPLICABLE TO THE DEVICE	METHOD OF CONFORMITY	IDENTITY OF SPECIFIC DOCUMENTS	GUIDANCE FOR THE MANUFACTURER OF THE DEVICE	RELEVANT HARMONISED STANDARDS
scale (including colour change and other visual indicators) must be designed and manufactured in line with ergonomic principles, taking account of the intended purpose of the device.					
4. Devices which are instruments or apparatus with a measuring function					
4.1 Devices which are instruments or apparatus having a primary analytical measuring function must be designed and manufactured in such a way as to provide adequate stability and accuracy of measurement within appropriate accuracy limits, taking into account the intended purpose of the device and of available and appropriate measurement procedures and materials. The accuracy limits have to be specified by the manufacturer.				The manufacturer should have evidence to support the accuracy of measurement and defined accuracy limits of the product. The details of the maintenance and calibration of the product should be described in the Instructions for Use.	
4.2 When values are expressed					

ESSENTIAL PRINCIPLE	APPLICABLE TO THE DEVICE	METHOD OF CONFORMITY	IDENTITY OF SPECIFIC DOCUMENTS	GUIDANCE FOR THE MANUFACTURER OF THE DEVICE	RELEVANT HARMONISED STANDARDS
numerically, they must be given in legal units conforming to the provisions of Council Directive 80/181/EEC of 20 December 1979 on the approximation of laws of the Member States relating to units of measurement.					
5. Protection against radiation					
5.1 Devices shall be designed and manufactured and packed in such a way that exposure of users and other persons to the emitted radiation is minimized.				This provision covers all forms of radiation, e.g. RIA tests and instruments.	
5.2 When devices are intended to emit potentially hazardous, visible and/or invisible radiation, they must as far as possible be: designed and manufactured in such a way as to ensure their characteristics and the quantity of radiation emitted can be controlled and/or adjusted; fitted with visual displays and/or audible warnings of such emissions.					

ESSENTIAL PRINCIPLE	APPLICABLE TO THE DEVICE	METHOD OF CONFORMITY	IDENTITY OF SPECIFIC DOCUMENTS	GUIDANCE FOR THE MANUFACTURER OF THE DEVICE	RELEVANT HARMONISED STANDARDS
5.3 The operating instructions for devices emitting radiation must give detailed information as to the nature of the emitted radiation, means of protecting the user, and on ways of avoiding misuse and of eliminating the risks inherent in installation.					
6. Requirements for medical devices connected to or equipped with an energy source					EN 61010-2-101:2002 (Safety requirements for electrical equipment for measurement, control, and laboratory use - Part 2-101: Particular requirements for *in-vitro* diagnostic medical equipment)
6.1 Devices incorporating electronic programmable systems, including software, must be designed to ensure the repeatability, reliability and performance of these systems according to the intended use.				The manufacturer should provide evidence to support the performance and repeatability of electronic programmable systems.	

ESSENTIAL PRINCIPLE	APPLICABLE TO THE DEVICE	METHOD OF CONFORMITY	IDENTITY OF SPECIFIC DOCUMENTS	GUIDANCE FOR THE MANUFACTURER OF THE DEVICE	RELEVANT HARMONISED STANDARDS
6.2 Devices must be designed and manufactured in such a way as to minimize the risks of creating electromagnetic perturbation which could impair the operation of other devices or equipment in the usual environment.				Reference should be made to Council Directive on the approximation on the laws of Member States relating to electromagnetic compatibility 89/336/EEC.	
6.3 Devices must be designed and manufactured in such a way as to avoid, as far as possible, the risk of accidental electric shocks during normal use and in single fault condition, provided the devices are installed and maintained correctly.					
6.4 Protection against mechanical and thermal risks					
6.4.1 Devices must be designed and manufactured in such a way as to protect the user against mechanical risks. Devices must be sufficiently stable under the foreseen operating conditions. They must be suitable to withstand stresses inherent					EN 61010-2-101:2002 (Safety requirements for electrical equipment for measurement, control, and laboratory use - Part 2-101: Particular

ESSENTIAL PRINCIPLE	APPLICABLE TO THE DEVICE	METHOD OF CONFORMITY	IDENTITY OF SPECIFIC DOCUMENTS	GUIDANCE FOR THE MANUFACTURER OF THE DEVICE	RELEVANT HARMONISED STANDARDS
to the foreseen working environment, and to retain this resistance during the expected life of the devices, subject to any inspection and maintenance requirements as indicated by the manufacturer. Where there are risks due to the presence of moving parts, risks due to break-up or detachment, or leakage of substances, then appropriate protection means must be incorporated. Any guards or other means included with the device to provide protection, in particular against moving parts, must be secure and must not interfere with access for the normal operation of the device, or restrict routine maintenance of the device as intended by the manufacturer.					requirements for *in-vitro* diagnostic medical equipment)
6.4.2 Devices must be designed and manufactured in such a way as to reduce to the lowest possible level the risks arising from vibration generation by the					

ESSENTIAL PRINCIPLE	APPLICABLE TO THE DEVICE	METHOD OF CONFORMITY	IDENTITY OF SPECIFIC DOCUMENTS	GUIDANCE FOR THE MANUFACTURER OF THE DEVICE	RELEVANT HARMONISED STANDARDS
devices, taking account of technical progress and of the means available for limiting vibrations, particularly at source, unless the vibrations are part of the specified performance.					
6.4.3 Devices must be designed and manufactured in such a way as to reduce as far as possible the risks arising from the noise emitted, taking account of technical progress and of the means available to reduce noise, particularly at source, unless the noise emitted is part of the specified performance.					
6.4.4 Terminals and connectors to electricity, gas or hydraulic and pneumatic energy supplies which the user has to handle must be designed and manufactured in such a way as to minimize all possible risks.					
6.4.5 Accessible parts of the devices (excluding the parts or areas intended to supply heat or reach given temperatures)					

ESSENTIAL PRINCIPLE	APPLICABLE TO THE DEVICE	METHOD OF CONFORMITY	IDENTITY OF SPECIFIC DOCUMENTS	GUIDANCE FOR THE MANUFACTURER OF THE DEVICE	RELEVANT HARMONISED STANDARDS
and their surroundings must not attain potentially dangerous temperatures under normal use.					
7. Requirements for devices for self-testing					
7.1 Devices for self-testing must be designed and manufactured in such a way that they perform appropriately for their intended purpose taking into account the skills and the means available to users and the influence resulting from variation that can reasonably be anticipated in users' technique and environment. The information and instructions provided by the manufacturer should be easily understood and applied by the user.					EN 13532:2002 (General requirements for *in-vitro* diagnostic medical devices for self-testing)
7.2 Devices for self-testing must be designed and manufactured in such a way as to: ensure that the device is easy to use by				The performance evaluation should include a population of lay-people. Misinterpretation or misuse of the self-testing product should be recorded.	EN 13532:2002 (General requirements for *in-vitro* diagnostic medical devices for self-testing)

ESSENTIAL PRINCIPLE	APPLICABLE TO THE DEVICE	METHOD OF CONFORMITY	IDENTITY OF SPECIFIC DOCUMENTS	GUIDANCE FOR THE MANUFACTURER OF THE DEVICE	RELEVANT HARMONISED STANDARDS
the intended lay-user at all stages of the procedure, and reduce as far as practicable the risk of user error in the handling of the device and in the interpretation of the results.					
7.3 Devices for self-testing must, where reasonably possible, include user control, i.e. a procedure by which the user can verify that, at the time of use, the product will perform as intended.					EN 13532:2002 (General requirements for *in-vitro* diagnostic medical devices for self-testing)
8.Information supplied by the manufacturer					
8.1 Each device must be accompanied by the information needed to use it safely and properly, taking account of the training and knowledge of the potential users, and to identify the manufacturer. This information comprises the data on the label and in the instructions for use. As far as practicable and appropriate, the information needed to use the device				Reference to the harmonised standards should be used.	EN 375:2001 (Information supplied by the manufacturer with *in-vitro* diagnostic reagents for professional use) EN 376:2002 (Information supplied by the manufacturer

ESSENTIAL PRINCIPLE	APPLICABLE TO THE DEVICE	METHOD OF CONFORMITY	IDENTITY OF SPECIFIC DOCUMENTS	GUIDANCE FOR THE MANUFACTURER OF THE DEVICE	RELEVANT HARMONISED STANDARDS
safely and properly must be set out on the device itself and/or, where appropriate, on the sales packaging. If individual full labelling of each unit is not practicable, the information must be set out on the packaging and/or in the instructions for use supplied with one or more devices. Instructions for use must accompany or be included in the packaging of one or more devices. In duly justified and exceptional cases no such instructions for use are needed for a device if it can be used properly and safely without them.					with *in vitro* diagnostic reagents for self-testing) EN 591:2001 (Instructions for use for *in-vitro* diagnostic instruments for professional use) EN 592:2002 (Instructions for use for *in-vitro* diagnostic instruments for self-testing)
8.2 Where appropriate, the information to be supplied should take the form of symbols. Any symbol and identification colour used must conform to the harmonized standards. In areas for which no standards exist, the symbols and colours must be described in the					EN 980:2003 (Graphical symbols for use in the labelling of medical devices)

ESSENTIAL PRINCIPLE	APPLICABLE TO THE DEVICE	METHOD OF CONFORMITY	IDENTITY OF SPECIFIC DOCUMENTS	GUIDANCE FOR THE MANUFACTURER OF THE DEVICE	RELEVANT HARMONISED STANDARDS
documentation supplied with the device.					
8.3 In the case of devices containing a substance or a preparation which may be considered as being dangerous, taking account of the nature and quantity of its constituents and the form under which they are present, relevant danger symbols and labelling requirements of Directive 67/548/EEC and Directive 88/379/EEC shall apply. Where there is insufficient space to put all information on the device itself or on its label, the relevant danger symbols shall be put on the label and the other information required by those Directives shall be given in the instructions for use. The provisions of aforementioned directives on the safety data sheet shall apply, unless all relevant information as appropriate is already made available by the instructions for use.				The labelling requirements of Council Directives 67/548/EEC and 88/379/EEC for devices containing a dangerous substance should be followed.	
8.4 The label must bear the following					EN 980:2003 (Graphical

ESSENTIAL PRINCIPLE	APPLICABLE TO THE DEVICE	METHOD OF CONFORMITY	IDENTITY OF SPECIFIC DOCUMENTS	GUIDANCE FOR THE MANUFACTURER OF THE DEVICE	RELEVANT HARMONISED STANDARDS
particulars which may take the form of symbols as appropriate: the name or trade name and address of the manufacturer. For devices imported into the Community with a view to their distribution in the Community, the label, the outer packaging, or the instructions for use, shall contain in addition the name and address of the authorized representative of the manufacturer established within the Community; the details strictly necessary for the user to uniquely identify the device and the contents of the packaging; where appropriate, the word 'STERILE' or a statement indicating any special microbiological state or state of cleanliness; the batch code, preceded by the word 'LOT' or the serial number; if necessary, an indication of the date by which the device or part of it should be					symbols for use in the labelling of medical devices)

ESSENTIAL PRINCIPLE	APPLICABLE TO THE DEVICE	METHOD OF CONFORMITY	IDENTITY OF SPECIFIC DOCUMENTS	GUIDANCE FOR THE MANUFACTURER OF THE DEVICE	RELEVANT HARMONISED STANDARDS
used, in safety, without degradation of performance, expressed as the year, the month and, where relevant, the day, in that order; in cases of devices for performance evaluation, the words 'for performance evaluation only'; where appropriate, a statement indicating the in vitro use of the device; any particular storage and/or handling conditions; where applicable, any particular operating instructions; appropriate warnings and/or precautions to take; k) if the device is intended for self testing, this fact should be clearly stated					
8.5 If the intended purpose of the device is not obvious to the user, the manufacturer must clearly state the intended purpose in the instructions for use and, if appropriate, on the label.					

ESSENTIAL PRINCIPLE	APPLICABLE TO THE DEVICE	METHOD OF CONFORMITY	IDENTITY OF SPECIFIC DOCUMENTS	GUIDANCE FOR THE MANUFACTURER OF THE DEVICE	RELEVANT HARMONISED STANDARDS
8.6 Wherever reasonable and practicable, the devices and separate components must be identified, where appropriate in terms of batches, to allow all appropriate action to detect any potential risk posed by the devices and detachable components.				The individual components and the overall kit itself should bear respective batch numbers to allow for traceability of the products.	
8.7 Where appropriate, the instructions for use must contain the following particulars: the details referred to in Section 8.4, with the exception of points d) and e); composition of the reagent product by nature and amount or concentration of the active ingredient(s) of the reagent(s) or kit as well as a statement, where appropriate, that the device contains other ingredients which might influence the measurement; the storage conditions and shelf life following the first opening of the primary container, together with the storage					EN 375:2001 (Information supplied by the manufacturer with *in-vitro* diagnostic reagents for professional use) EN 376:2002 (Information supplied by the manufacturer with *in-vitro* diagnostic reagents for self-testing) EN 591:2001 (Instructions for use *in-vitro* diagnostic

ESSENTIAL PRINCIPLE	APPLICABLE TO THE DEVICE	METHOD OF CONFORMITY	IDENTITY OF SPECIFIC DOCUMENTS	GUIDANCE FOR THE MANUFACTURER OF THE DEVICE	RELEVANT HARMONISED STANDARDS
conditions and stability of working reagents; the performances referred to in Section 3 an indication of any special equipment required including information necessary for the identification of that special equipment for proper use; the type of specimen to be used, any special conditions of collection, pre-treatment and, if necessary, storage conditions and instructions for the preparation of the patient; a detailed description of the procedure to be followed in using the device; the measurement procedure to be followed with the device including as appropriate : the principle of the method; the specific analytical performance characteristics (e.g. sensitivity, specificity, accuracy, repeatability, reproducibility, limits of detection and measurement					instruments for professional use) EN 592:2002 (Instructions for use *in-vitro* diagnostic instruments for self-testing)

ESSENTIAL PRINCIPLE	APPLICABLE TO THE DEVICE	METHOD OF CONFORMITY	IDENTITY OF SPECIFIC DOCUMENTS	GUIDANCE FOR THE MANUFACTURER OF THE DEVICE	RELEVANT HARMONISED STANDARDS
range, including information needed for the control of known relevant interferences), limitations of the method and information about the use of available reference measurement procedures and materials by the user; the details of any further procedure or handling needed before the device can be used (for example reconstitution, incubation, dilution, instrument checks, etc.); the indication whether any particular training is required; the mathematical approach upon which the calculation of the analytical measurement is made; measures to be taken in the event of changes in the analytical performance of the device; information on internal quality control including specific validation procedures,					

ESSENTIAL PRINCIPLE	APPLICABLE TO THE DEVICE	METHOD OF CONFORMITY	IDENTITY OF SPECIFIC DOCUMENTS	GUIDANCE FOR THE MANUFACTURER OF THE DEVICE	RELEVANT HARMONISED STANDARDS
the traceability of the calibration of the device and the reference intervals for the quantities being determined, including a description of the appropriate reference population; if the device must be used in combination with or installed with or connected to other medical devices or equipment in order to operate as required for its intended purpose, sufficient details of its characteristics to identify the correct devices or equipment to use in order to obtain a safe and proper combination; all the information needed to verify whether the device is properly installed and can operate correctly and safely, plus details of the nature and frequency of the maintenance and calibration needed to ensure that the device operates properly and safely; information about safe waste disposal; details of any further treatment or					

ESSENTIAL PRINCIPLE	APPLICABLE TO THE DEVICE	METHOD OF CONFORMITY	IDENTITY OF SPECIFIC DOCUMENTS	GUIDANCE FOR THE MANUFACTURER OF THE DEVICE	RELEVANT HARMONISED STANDARDS
handling needed before the device can be used (for example, sterilization, final assembly, etc.); the necessary instructions in the event of damage to the special protective packaging and, details of appropriate methods of resterilization or decontamination; if the device is reusable, information on the appropriate processes to allow reuse, including cleaning, disinfection, packaging and resterilization or decontamination, and any restriction on the number of reuses; precautions to be taken as regards exposure, in reasonably foreseeable environmental conditions, to magnetic fields, external influences, electrostatic discharge, pressure or variations in pressure, acceleration, thermal ignition sources, etc.; precautions to be taken against any					

ESSENTIAL PRINCIPLE	APPLICABLE TO THE DEVICE	METHOD OF CONFORMITY	IDENTITY OF SPECIFIC DOCUMENTS	GUIDANCE FOR THE MANUFACTURER OF THE DEVICE	RELEVANT HARMONISED STANDARDS
special, unusual risks related to the use or disposal of the device including special protective measures; where the device includes substances of human origin, attention shall be drawn to their potential infectious nature; specifications for devices for self-testing: the results need to be expressed and presented in a way that is readily understood by a lay person; information needs to be provided with advice to the user on action to be taken (in case of positive, negative or indeterminate result) and on the possibility of false positive or false negative results; specific particulars may be omitted provided that the other information supplied by the manufacturer is sufficient to enable the user to know how to use the device and to understand the result(s) produced by the device; the information provided must include a					

ESSENTIAL PRINCIPLE	APPLICABLE TO THE DEVICE	METHOD OF CONFORMITY	IDENTITY OF SPECIFIC DOCUMENTS	GUIDANCE FOR THE MANUFACTURER OF THE DEVICE	RELEVANT HARMONISED STANDARDS
statement clearly directing that the user should not take any decision of medical relevance without first consulting his or her medical practitioner; the information must also specify that when the device for self-testing is used for the monitoring of an existing disease, the patient should only adapt the treatment if he has received the appropriate training to do so; date of issue or last revision of the instructions for use.					