The EU IVD Directive (98/79 EC) - a user's point of view

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The Directive is a complex and detailed document and in the following the author focuses on some of the items that are particularly important for the user to be aware of.

Most of the rules will apply to the manufacturers and the public and the users will take advantage of the rulings if they become aware of their existence. The reader is referred to the document for a complete picture and to the references (1-6). The latter do, however, view the Directive mainly from an industry perspective.

The Directive comprises 24 separate Articles and 10 Annexes. The present text will only highlight the most important items with a view to familiarize the reader with the thoughts of the Directive. These are as follows:

- Article 1; Scope and definitions
- Article 3; Essential requirements (Annex I)
- Article 9; Conformity assessment procedure (Annex II)
- Article 11; Vigilance procedure

Many of the clauses of the Directive simply comply with and emphasize established good laboratory practice of serious manufacturers and users, but it is clearly of great importance that these principles are laid down in an EU directive.

Other parts of the text and clauses of the Directive lend themselves to interpretations; some of these points will be highlighted but generally the author refrains from giving his own views of the Directive.

Background

The EU lawmakers create 'Directives' to coordinate and harmonize various activities in the European Union.

The last in a series of important Directives that affect Laboratory Medicine is the 'Directive 98/79/EC of the European Parliament and of the Council of 27 October 1998 on *in vitro* Diagnostic Medical Devices', in short the IVD Directive.

After a stepwise introductory period of five years it will come into full power for placing on the market by December 7, 2003 with all its rules and amendments.

The Directive was developed over several years and is still not easy to comprehend in all its details. It outlines the obligations of the manufacturer and the performance of laboratory instruments and reagents in general terms.

Necessary practical details are then supposed to be further considered in written standards and other documents by a Committee on Standards and Technical Regulations.

For this purpose the Technical Committee 140 of the European Committee for Standardization (CEN TC 140) '*In vitro* Diagnostic Medical Devices' has been created. The CEN TC 140 has been working through nine different working groups and began its work before the Directive became official.

The completed standards are listed in **Table I**. Several of these standards have been developed in collaboration with the ISO Technical Committee 212 (Clinical Laboratory Testing and *in vitro* Diagnostic Test Systems), e.g. the ISO 15189:2003, and thus become of global interest and importance.

Purpose

The Directive was written to 'harmonize and satisfy health protection and performance, characteristics and authorization procedures for *in vitro* diagnostic medical devices (IVDs) and thus facilitate the removal of trade barriers between the countries of the EU due to legislative disparities'.

It therefore 'lays down only such requirements as are necessary and sufficient to ensure, under the best safety conditions, free movement of the *in vitro* diagnostic medical devices to which it applies'. The two guiding principles of the Directive are clearly stated:

- 1. to provide patients, users and third parties with a high level of health protection and
- 2. attain the performance levels originally attributed to them by the manufacturer.

Only IVDs that fulfill the criteria of the Directive may

be CE-marked and the CE-mark must be affixed to products when they are placed on the European market.

Only CE-marked devices may be introduced in medical laboratories after December 7, 2003, although there is a transition period for devices used by the laboratory before that date. The CE-mark indicates that the product meets the essential requirements that are spelled out in Article 3 and Annex 1.

From the users' point of view these essential requirements are the nucleus of the directive. The competent Member State shall take appropriate action against those that affix the CE-marking to a non-complying device.

Scope and definitions (Article 1)

The scope of the Directive is spelled out in the first article. Some of the seven sections and 10 subsections will be cited:

The Directive shall apply to *in vitro* diagnostic medical devices and their accessories. It is not, however, quite clear, even to the professional, what would be included in that concept, and accordingly the Directive spells out what is meant in a series of definitions. Below is an abbreviated list of the most important definitions that may facilitate the understanding of the Directive.

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

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

and which does not achieve its principal intended action in or on the human body by pharmacological, immunological, or metabolic means. The specification '*in vitro* diagnostic medical device' (IVD) means any medical device which is a reagent, reagent product, calibrator, control material, kit, instrument, apparatus, equipment, or system, whether used alone or in combination, intended by the manufacturer to be used *in vitro* for the examination of specimens, including blood and tissue donations, derived from the human body solely or principally for the purpose of providing information:

- concerning a physiological or pathological state, or
- concerning a congenital abnormality, or
- to determine the safety and compatibility with potential recipients, or
- to monitor therapeutic measures.

The Directive lists specimen receptacles (e.g. blood collection tubes) as IVDs but excludes products for general laboratory use (e.g. laboratory utensils).

'Accessory' means an article which, whilst not being an IVD is intended specifically by its manufacturer to be used together with a device to enable that device to be used in accordance with its intended purpose.

Invasive sampling devices or those which are directly applied to the human body for the purpose of obtaining a specimen within the meaning of another Directive (93/42/EEC) shall not be considered accessories.

'Device for self-testing' means any device intended by the manufacturer to be used by lay persons in a home environment.

'Device for performing evaluation' means any device intended by the manufacturer to be subject to one or more performance evaluation studies in laboratories.

'Intended purpose' means the use for which the device is intended according to the data supplied by the manufacturer on the labeling, in the instructions for use and/or in promotional material.

'Placing on the market' means that first making available in return for payment or free of charge of a device other than a device intended for the performance evaluation, and that 'putting into service' means the stage at which a device has been made available to the end user on the Community market for the first time as being ready for use for its intended purpose.

'*Calibration and control materials*' refer to any substance, material, or article intended by their manufacturer either to establish measurement relationships or to verify the performance characteristics of a device in conjunction with the intended use of that device.

According to the scope, the Directive excludes devices (including accessories) that are used only within the same health institution and on the premises of their manufacture or used on premises in the immediate vicinity without having been transferred to another legal entity.

Essential requirements (Article 3 and Annex I)

Operatively, the 'essential requirements' in Annex I are fundamental to the Directive and devices must meet these criteria, taking account of the intended purpose of the devices concerned.

General requirements

The general requirements section of the Annex states, in five sections, various precautions that the manufacturer has to observe to ascertain that the device, when used under the conditions and for the purpose intended, in its design and manufacturing, does not directly or indirectly compromise the clinical condition of a patient, the safety of the user, or the safety of the property.

It goes on to state the responsibility of the manufacturer to eliminate or reduce risks and inform users of any remaining risks. The devices must achieve the performances, in particular in terms of analytical and diagnostic sensitivity and specificity, trueness and precision (reproducibility and repeatability), 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 reference measurement procedures and/or available reference materials of a higher order.

Chemical, physical, mechanical, thermal, radiation, and electrical risks shall be minimized, environmental and ergonomic effects shall be considered and any adverse effects minimized.

Requirements for instruments with measuring function

The Directive also demands that the IVDs that are instruments with measuring functions shall be designed and manufactured in such a way as to provide adequate stability and accuracy (trueness and precision) within appropriate limits.

The manufacturer shall specify the accuracy limits. Results, when expressed numerically, must be given in legal units conforming to provisions of a Council directive (80/181/EEC).

Requirements for self-testing devices

IVDs for self-testing shall comply with all the risk precautions above, but in addition be safe in the hands of laypersons. The Directive also states that these devices shall advise procedures by which the user can verify that the product will perform as intended.

Information supplied by the manufacturer

An important section of the essential requirements deals with the responsibility of the manufacturer to supply the information needed for safe and proper use and to identify the manufacturer. Information shall be given on the device itself and/or when appropriate, on the sales package.

The Directive favors that warnings and other information are given as symbols, when available, and there are detailed requirements for the necessary contents on labels as well as the minimal information provided as instructions for use.

The label shall show details that are strictly necessary for the user to uniquely identify the device and the contents of the packaging, the batch or the serial number shall be given.

It has been debated to what extent the user may rewrite or modify the instructions for use without violating the Directive or the intentions of the Directive. It has been argued that this will free the manufacturer from responsibility for the proper function of the device.

The Directive details in 21 statements what information shall be available to the user. This list comprises practically all possible characteristics of reagents and instrument.

A consequence will be that laboratories can limit, or even omit, the validation processes when taking a CEmarked device into service and concentrate on verifying the specifications. Verification is a much less demanding procedure than validation and facilitates the evaluation of instruments, reagents, and procedures.

The instructions for use must also contain a description of the measurement procedure that should be followed, its analytical performance characteristics and particular training.

A standardized protocol that could be applied to most instruments and procedures would most likely simplify the writing process for the laboratories and largely eliminate the demand for local and customized instructions for use. A starting point of such a standard might be EN 12286:2000.

The biological reference intervals, including a description of the reference population, are required. This will require an extensive collaboration with the professional, but it is foreseen that the industry may face difficulties when creating reference intervals that can be used globally.

Therefore, the accreditation standard for medical

laboratories, the EN/ISO 15189:2003 'Medical laboratories - Particular requirements for quality and competence' (See also "Accreditation of medical laboratories using ISO 15189:2003" by René Dybkær on www.acutecaretesting.org) states that the accredited laboratories shall establish their own reference intervals.

This is a very heavy burden for laboratories and should be a topic for coordinated initiatives. Common reference intervals require that the results of measurements in different laboratories are transferable.

Interestingly, the mathematical approach upon which the calculation of the analytical result is made must be disclosed as well as information on internal quality control and validation procedures and the traceability of the calibration of the device.

Language requirements

In the original text of the directive there is no reference to providing information in local languages.

However, in an important addition to the point Annex I B 8.1 from 1998 it is stated that the 'decision whether to translate the instructions for use and the label into one or more languages of the EU shall be left to the Member States, except that, for devices for self-testing, the instructions for use and the label must include a translation into the official language(s) of the member State in which the device for self-testing reaches its final use'.

As a user, one would welcome an extended interpretation that all information that is necessary for the immediate operation should be in a language that is commonly understood in the laboratory.

Conformity assessment procedure (Article 9 and Annex II)

Annex II with the intriguing title 'List of devices referred to in article 9(2) and (3)' contains two lists; A and B. But first let us visit Article 9 that deals with 'Conformity assessment procedures'. According to this article the manufacturer alone is obliged to and responsible for all the documentation that is necessary to fully describe the product in accordance with the EC declaration of conformity, detailed for IVDs in Annex II of this Directive.

The rules that are applied are described in Annexes IV and V. Besides detailed instructions in the Annexes, the Directive rules that the quality of the products listed in these Annexes shall be assessed and certified by a competent 'notified body'.

The criteria and qualifications and tasks for a notified body are spelled out in Annex IX with the additions and amendments listed in Article 21 of the main text.

The CE-mark that will be affixed to the product will include a four-digit number that identifies the product and/or the notified body. The contents of Annex II may be modified according to Article 14 that rules how amendments should be made.

It expands Annex II by stating that amendments shall be made with due consideration given to inter alia 'whether total reliance has to be placed on the result obtained with a given device and if the result will have a direct impact on subsequent medical action and whether the involvement of a notified body would be conducive to establishing the conformity of the device'.

Vigilance procedure (Article 11)

The Member States - and thus the users - shall presume compliance with the essential requirements in respect of devices that are in conformity with the relevant national standards. If for duly justified reasons manufacturers do not comply with those specifications they must adopt solutions of a level at least equivalent to them.

The directive addresses the possible malfunction of IVDs in Articles 8 and 11. The first article is a safeguard clause that allows the Member States to take all appropriate interim measures to withdraw such devices from the market that, when correctly installed, maintained, and operated, may compromise the health/or safety of patients, users, or properties. The second article rules that Member States shall take the necessary steps to ensure that any information that is brought to its knowledge regarding certain incidents and involving CE-marked products are recorded and evaluated centrally.

To qualify, the incidents must be serious and 'might lead to or might have led to the death of patient, or user or of other persons or to a serious deterioration in the state of health'. A comprehensive guidance document (MEDDEV 2.12, rev 2001) that describes various aspects on the vigilance system has been published by the EU [7].

It is important that information on such incidents shall be brought to medical institutions, organizers of External Quality Assessment Schemes (EQAS), and also the manufacturer of the device concerned.

After carrying out of an assessment, if possible together with the manufacturer, the Member State shall immediately inform the Commission and other Member States of the measures taken.

Conclusions

The Directive details the requirements of *in vitro* diagnostic devices to a useful level. The Directive itself and the Standards that have been or are presently being developed by the CEN Technical Committee 140 alone or in collaboration with the ISO Technical committee 212 will further improve the reliability and practicability of instruments and reagents used in medical laboratories and by laymen for home use.

The complexity of the Directive and the emerging Standards reflects the expectations of medical laboratories and prompts manufacturers and users alike to become familiar with the demands of modern good laboratory practice.

The most important demands for the user to be familiar with are the essential requirements (Article 3 and Annex I), especially the information supplied by the manufacturer that enables the laboratory to verify the specifications and reference intervals, but also how to behave if a CE-marked product does not fulfill the IVD requirements or is involved in critical incidents.

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 for in vitro diagnostic instruments for professional use
EN 592:2002	Instructions for use for in vitro diagnostic instruments for self-testing
EN 12286:2000	<i>In vitro</i> diagnostic medical devices - Measurement of quantities in samples of biological origin - Presentation of reference measurement procedures
EN 12287:1999	<i>In vitro</i> diagnostic medical devices - Measurements of quantities in samples of biological origin - Description of reference materials
EN 12322:1999	In vitro diagnostic medical devices - Culture media for microbiology - Performance criteria for culture media
EN 12376:1999	In vitro diagnostic medical devices - Information supplied by the manufacturer with in vitro diagnostic reagents for staining in microbiology
EN 3640:2002	Stability testing of <i>in vitro</i> diagnostic reagents
EN 3641:2002	Elimination or reduction of risk of infection related to in vitro diagnostic reagents
EN ISO 15189	Medical laboratories - Particular requirements for quality and competence
prEN ISO 15195	Clinical laboratory medicine - Requirements for reference measurement laboratories
prEN ISO 15197	<i>In vitro</i> diagnostic test systems - Requirements for blood-glucose monitoring systems for self-testing in managing diabetes mellitus
prEN ISO 17511	<i>In vitro</i> diagnostic medical devices - Measurements of quantities in samples of biological origin - Metrological traceability of values assigned to calibrators and control materials
prEN ISO 18153	<i>In vitro</i> diagnostic medical devices - Measurement of quantities in samples of biological origin - Metrological traceability of values for catalytic concentration of enzymes assigned to calibrators and control materials

TABLE I: Standards that have been prepared by CEN/TC 140 (as listed on the CEN web-site 03-06-27). Documents with EN-numbers have been ratified through the CEN voting procedure, those with prEN have not yet been finally approved and those with EN/ISO have been developed together with the ISO/TC 212.

References

- Dati F, Kupp C. The European Directive 98/79/EC on *in* vitro Diagnostic Medical Devices. J Lab Med 2000;24:40-51
- Directive 98/79/EC to the European Parliaments and of the Council 1998-10-27 on in vitro Diagnostic Medical Devices. Official J of the European Communities 1998; 331:1-37.
- 3. Gower G. Coping with the IVD Directive. Med Device Technol 2000;11,8:28-9.
- Powers DM. Towards global *in vitro* diagnostic standards, Part I. Med Device Technol 2000; 11,3:34-7.
- 5. Powers DM. Towards global in vitro diagnostic standards, Part II. Med Device Technol 2000; 11,4:41-4.
- 6. Spencer S. Performance evaluation and the IVD directive. Med Device Technol 2002; 13,9: 41-3
- Guidelines on a medical Devices Vigilance system. EC DG Enterprise Directorate G, Unit 4. http://europa.eu.int/ comm/enterprise/medical_devices guidelinesmed/2_12-1 ___04-2001.pdf, MEDDEV 2.12 - rev 4 April 2001