Austria
Abbott Ges.m.b.H.
Diagnostics
Tel. (+43) 1 89 122 0
Fax (+43) 1 89 122 44

Belgium/Luxembourg
Abbott S.A./N.V.
Tel. (+32) 10 47 53 11
Fax (+32) 10 47 53 34

Croatia
Abbott Representative
Office
Tel. (+385) 1 23 50 560
Fax (+385) 1 24 41 331

Czech Republic
Abbott Laboratories s r.o.
Tel. (+420) 2 672 92 111
Fax (+420) 2 672 92 233

Denmark
Abbott Laboratories A/S
Diagnostics
Tel. (+45) 39 77 00 00
Fax (+45) 39 77 01 99

Egypt (MEN)
ADD Egypt
Tel. (+20) 2 2 68 49 31
Fax (+20) 2 2 68 49 21

Finland
Abbott Oy/Diagnostics
Tel. (+358) 9 75 18 42 1
Fax (+358) 9 75 18 41 50

France
Abbott France S.A.S.
Tel. (+33) 1 45 60 25 00
Fax (+33) 1 45 60 04 98

Germany
Abbott GmbH & Co. KG
Tel. (+49) 6122 580
Fax (+49) 6122 581244

Greece
Abbott Laboratories
(Hellas) S.A.
Tel. (+30) 2 10 99 85 171
Fax (+30) 2 10 99 58 361

Hungary
Abbott Kft.
Tel. (+36) 1 465 2100
Fax (+36) 1 465 2199

Ireland
Abbott Diagnostics
Tel. (+353) 1 469 1560
Fax (+353) 1 469 1565

Italy
Abbott S.p.A.
Abbott Diagnostici
Tel. (+39) 06 52 99 11
Fax (+39) 06 52 99 14 36

Latvia
Abbott Laboratories S.A.
Latvian Representative
Office
Tel. (+371) 7 31 48 23
Fax (+371) 7 31 48 38

Netherlands
Abbott B.V.
Tel. (+31) 23 55 44 500
Fax (+31) 23 55 44 577

Norway
Abbott Norge AS
Tel. (+47) 81 55 99 20
Fax (+47) 67 11 31 49

Poland
Abbott Laboratories
Poland Sp. z o.o.
Tel. (+48) 22 606 10 50
Fax (+48) 22 606 10 80

Portugal
Abbott Laboratòrios Lda.
Diagnòsticos
Tel. (+351) 21 472 72 00
Fax (+351) 21 472 72 00

Romania
Abbott Laboratories
Representative Office
Romania
Tel. (+4021) 3 36 86 00
Fax (+4021) 3 36 86 42

Russian Federation
Abbott Laboratories S.A.
Tel. (+7) 0952 5842 70
Fax (+7) 0952 5842 71

Saudi Arabia
Mediserv
Tel. (+966) 14 6122 26
Fax (+966) 14 6133 39

Slovak Republic
Abbott Laboratories
Slovakia s r.o.
Tel. (+421) 244 454 188
Fax (+421) 244 454 420

South Africa
Abbott Laboratories
(Pty) Ltd.
Tel. (+27) 11 858 2000
Fax (+27) 11 858 2130

Spain
Abbott Científica S.A.
Tel. (+34) 91 337 3400
Fax (+34) 91 734 9664

Sweden
Abbott Scandinavia AB
Tel. (+46) 8 5465 6700
Fax (+46) 8 5465 6800

Switzerland
Abbott AG
Diagnostics
Tel. (+41) 41 768 44 44
Fax (+41) 41 768 44 50

Turkey
Abbott Laboratuarlari
Tel. (+90) 216 5 38 74 00
Fax (+90) 216 4 25 09 78

United Arab Emirates
Abbott Laboratories S.A.
Tel. (+971) 43 327 862
Fax (+971) 43 327 904

United Kingdom
Abbott Laboratories Ltd.
Diagnostics
Tel. (+44) 16 28 7840 41
Fax (+44) 16 28 6442 05

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AXXXXX/uk The European IVD Directive 08/04/X

The European In Vitro Diagnostic Directive

Harmonized Requirements for Diagnostic Products and Instruments in a Common European Market

ABBOTT

Introduction

Since December 7, 2003, only IVD products that are CE marked can be placed on the European market. The meaning of CE marking and the background to the requirements are described in this brochure. We hope that we can give you some more insight of this new regulatory requirement in the European Community. If you have any further question to this framework, we will be happy to respond to it.

Abbott Laboratories
Dr. Petra Kaars-Wiele
Director Regulatory Affairs/Affiliate Compliance
Europe, Middle East and Africa

Background

The European Union (EU) has created a Directive for *in-vitro* diagnostic reagents and kits, accessories and instruments by way of the *In-Vitro* Diagnostic Medical Device Directive 98/79/EC.
It provides

- a common European standard of safety in order to protect the level of health of the EU citizens
- the free movement of goods within the European Economic Area
- a single harmonized system of placing a product on the market instead of many different national systems and approvals.

Principles of CE Marking

The CE marking symbolizes the conformity of the product with the applicable Community requirements imposed on the manufacturer. The CE marking affixed to products is a declaration by the responsible person that:

- the product conforms to all applicable Community provisions
- the product meets the Essential Requirements of the Directive, and
- the appropriate conformity assessment procedures have been completed.

"CE" stands for **C**onformité **E**uropéenne, the French word for:
European Conformity.

What is an IVD Medical Device

The definition from the Directive says: "'*in-vitro* diagnostic medical device' means any medical device which is a reagent, reagent product, calibrator, control material, kit, instrument, apparatus, equipment, or system, whether used alone or in combination, intended by the manufacturer to be used *in-vitro* for the examination of specimens, including blood and tissue donations, derived from the human body, solely or principally for the purpose of providing information:

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

Specimen receptacles are considered to be *in-vitro* diagnostic medical devices. They are specifically intended by their manufacturers for the primary containment and preservation of specimens derived from the human body for the purpose of *in-vitro* diagnostic examination.

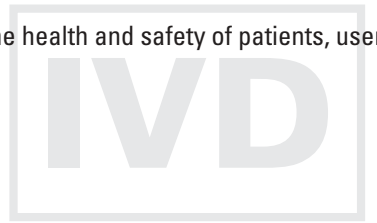
Products for general laboratory use are not *in-vitro* diagnostic medical devices ...” (examples: pipettes, laboratory glass ware, centrifuges, common wash buffers or devices which have no claim for IVD use, but broadly used for general laboratory use)

The Scope of the *In-Vitro* Diagnostic Directive

Since December 7, 2003 all *in-vitro* diagnostic products, which are placed on the market of the European Economic Area, have to comply with the requirements of the Directive.

IVD products, which had been placed on the market before December 7, 2003, can be put into service by the end users until December 6, 2005.
The Directive describes comprehensively, which Essential Requirements a product must satisfy. These aim to ensure that the products

- are designed and manufactured in a way to achieve the specified performance
- and do not compromise the health and safety of patients, users and protect the environment



Which Countries Have Transposed the IVD Directive?

All EU countries have transposed the Directive into national law: Austria, Belgium, Czech Republic, Cyprus, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxemburg, Malta, The Netherlands, Poland, Portugal, Slovak Republic, Slovenia, Spain, Sweden and UK. Other countries belonging to the European Free Trade Association (EFTA) have adapted the Directive as well: Iceland, Liechtenstein, Norway and Switzerland.
Outside the EU and EFTA, several countries have implemented the Directive or parts of it to harmonize with the European system or to prepare to join the EU at a later stage.

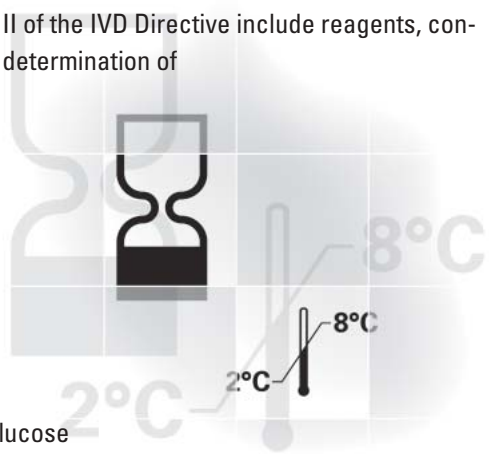
Which Products Fall Under the Directive?

Products have been categorized depending on the potential risk for the population or individuals.
In principle, there are 4 classes of *in-vitro* diagnostic products based on risk as follows

1. Annex II List A – highest risk
2. Annex II List B – high to medium risk
3. Self Test – medium risk
4. General category – low risk

High-risk products listed in Annex II of the IVD Directive include reagents, control and calibrator material for the determination of

- HIV-1/HIV-2
- HTLV I, HTLV-II
- Hepatitis B, C and D
- Rubella
- Toxoplasmosis
- CMV
- Chlamydia
- HLA DR, A and B
- PSA
- Self-testing devices for blood glucose
- Devices evaluating the risk for Trisomy 21



The products with "high risks" need to fulfill additional, very precisely specified quality requirements. Independent and competent third parties, like TÜV Product Services GmbH, Underwriter Laboratories or Lloyd's Register Quality Assurance accredited as "Notified Bodies", are required to assess the products and/or the quality system and provide CE compliance certificates for these products.

Self-testing devices (except those for blood glucose measurement mentioned above) have to be assessed for their suitability to be used by lay users. The design of these devices is subject to approval by a Notified Body.

All other IVDs are classified as "self-declared" by the manufacturers. In this case the manufacturer declares the conformity with the IVD Directive. No Notified Body is involved.

The Requirements

The IVD Directive has laid out the fundamental requirements that *in-vitro* diagnostic products have to comply with to be placed on the European market and to be approved for the free movement of goods within the European Community. The essential requirements devote particular attention to:

- safety for users, patients and the environment
- the performance level within the scope of the intended use
- the sensitivity and specificity.

A conformity assessment procedure – done by the Notified Body for Annex II products – is intended to prove that the technical performance and the intended purpose have been achieved. For "self-declared" products the manufacturers does the conformity assessment without involving a Notified Body.

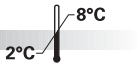
For Annex II List A products, Common Technical Specifications (CTS), which have been established by the EU Commission following consultation with Member States, industry and other stakeholders, ensure that products are state-of-the-art and comply with certain sensitivity and specificity levels. The CTS serve in particular as the basis for evaluation and batch verification. They describe what kind of samples or how many samples must be tested to prove that the assays under evaluation perform safely and efficiently and as intended.

Labeling Requirements and Symbols

Many countries have local language requirements and, due to small packages or vials, the manufacturer has to use symbols to reduce wording on the labels. Some of the symbols are described in the standard EN 980:2003, but the manufacturer may create further symbols, if needed. They must be explained in the instructions-for-use.

Here are some of the most common symbols used for IVDs:

 Expiration date



Storage temperature

 Refer to instruction-for-use

In-Vitro Diagnostic product

List number or product number

CE Mark with Notified Body identification

The Declaration of Conformity

The manufacturer must draw up a Declaration of Conformity (DOC). The Declaration should contain all relevant information to identify the applicable Directives, as well as the manufacturer, the Notified Body if applicable, the product, and where appropriate a reference to the harmonized standards. The Declaration of Conformity is a legal document that can be requested from manufacturers for all products fulfilling the requirements of the Directive.

Other Certificates

For Annex II List A products the Notified Body issues an EC (European Community) Design Examination Certificate (DEC) and an Approval of Conformity (AOC) as proof that the design of the products and the quality system have been assessed. For Annex II List B products only an Approval of Conformity is required. The design for these products is not assessed, but the quality system under which the product is manufactured and controlled.

Self-testing devices are checked for their proper design for use by laypersons and get an EC Design Examination Certificate from a Notified Body.
For all other IVD medical devices the Declaration of Conformity of the manufacturer is sufficient.

Post-Market Surveillance and Vigilance

The manufacturer is required to establish a program to monitor his products to ensure the safe handling of products and that the products perform as intended. The IVD Directive requires that manufacturers report medical incidents. Product malfunctions, which led or have the potential to lead to death, serious injury or deterioration in the state of health, must be reported to the Competent Authority in the country where the incident occurred. In addition, manufacturers must report any systematic recall to the authorities.

In general, Competent Authorities follow-up on any reported incident and in most cases the authority will contact the laboratory in their country with the aim to get further information/details about the incident. Based on the received information, there will be a follow-up with the manufacturer to define further corrective actions or the case will be closed.

Supervision by the Health Authorities

Surveillance audits by the Health Authorities (called Competent Authorities) in the member states where the manufacturer resides are done to ensure that manufacturers comply with the provisions of the Directive.

Health Authorities may verify that the affixing of the CE marking is correct. Where necessary, the authority has to take appropriate corrective actions to protect the CE marking. A Member State will have to notify the EU Commission and the other Member States if it decides to restrict free movement due to incorrect affixing of the CE marking, or when it takes action against those who are responsible for a non-compliant product bearing the CE marking.

A vigilance system ensures that national health authorities notify all other EU and EFTA Health Authorities about serious performance issues or inadequate instruction-for-use that can result, or have resulted in, the death of patients or users, or serious deterioration of their health.