European Diagnostic Manufacturers Association

EDMA position paper

Labelling of Devices Containing Radioactive Substances

13th October 2006.

Foreword

The intention of this position paper is to provide information for manufacturers on how to label *in vitro* diagnostic medical devices (IVDs) containing ionizing radiation. This is to ensure the safe use and handling of those devices, and to comply with the relevant requirements stemming from Directive 98/79/EC on *in vitro* diagnostic medical devices (IVD Directive) and from Directive 96/29/Euratom laying down basic safety standards for the protection of the health workers and the general public against the dangers arising from ionizing radiation.

Furthermore this document can be used to inform relevant authorities and/or stakeholders of the position of industry on this issue.

The need for this document was identified due to various different national requirements resulting from differing transpositions of directive 96/29/Euratom – where various member states are entitled to add requirements over and above those stated in Directive 96/29/Euroatom, and of the interpretation of what constitutes *"detailed information as to the nature of the emitted radiation"* as stated in annex I section B 5.3 of the Directive 98/79/EC.

Introduction

In the IVD Directive an essential requirement deals with protection against radiation (Annex I section B 5). The IVD Directive also states that IVDs will have to comply with Directive 96/29/Euratom laying down basic safety standards for the protection of the health workers and the general public against the dangers arising from ionizing radiation for those IVDs which include radioactive substances.

The only IVDs which use radioactive substances are radio-immunoassays (RIA). In these assays one of the reagents (an antigen or an antibody) is radioactively labelled so as to facilitate its detection. As with other IVDs, patients are never exposed to any of the reagents used in the assays, so there is no risk of exposure of patients to ionizing radiation from these assays – only laboratory professionals will use these assays. Furthermore the amounts of radioactive substances used in these assays are minor – often less than the amounts approved for injection to patients in other procedures.

The issue arises because of the nature of the Euratom Directive – different member states have transposed this directive in different manners and many have added requirements over and above those stated in the directive text itself. This is not a case of incorrect transposition. Within the framework of the Euratom Directive, Member States were entitled to introduce further requirements for safety in their national legislation. IVD manufacturers strive to use a single label throughout the whole of the EU.

The problem arises when an IVD manufacturer bases his labelling on the requirements which are stated either in their national legislation or the text of the Directive 96/29/Euratom – it is likely that

they will be out of compliance in other member states as the relevant national requirements may not always be addressed.

The objective of this guidance is to give industry recommendations for the labelling of IVDs containing radioactive isotopes so that they can be accepted throughout the EU. This document is based on an inquiry by EDMA into the labelling requirements throughout the EU as well as discussions with Competent Authorities responsible for Nuclear Safety.

Regulatory Implications

Concerning the labelling of devices emitting radiation the IVD Directive states the following (Annex I Section B, essential requirements)

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.

One of the differences in the application of this requirement of the IVD Directive is the level of information required on the nature of the emitted radiation, which is interpreted in different ways by competent authorities dealing with radiological protection.

It is worth also noting that the IVD Directive explicitly states in the considerants that:

13 […] Whereas this Directive does not affect the application of Council Directive 96/29/Euratom of 13 May 1996 laying down basic safety standards for the protection of the health of workers and the general public against the dangers arising from ionising radiation.

Therefore the labelling provision of Council Directive 96/29/Euratom are applicable to IVDs.

However, Council Directive 96/29/Euratom does not mention IVDs specifically anywhere in the text (though there are references to the administration of radioactive substances to persons for medical purposes and the use of radioactive sources for medical treatment) Nor does it lay down specific labelling requirements – however it does lay down a number of general principles on the safe use of radioactive sources. In transposing the directive, some member states add only generic labelling requirements (i.e. Italy, Germany, Austria) while other member states add requirements which are specific to IVDs (i.e. Belgium).

Labelling Requirements – Primary Label (Immediate Contariner)

All countries require the following on the primary label (label which is directly on the container which contains the radioactive substance)

1. The symbol for radioactivity: (may be red or black on a yellow background)

2. The isotope concerned (In the case of RIA this is most commonly ^{125}I)

3. The amount of radioactivity (in Bq)

4. In some member states it is also required to provide the nature of the labelled compound (i.e. to state whether it is an antigen or an antibody)

Taking all of the above into consideration the EDMA recommendation is for manufacturers to ensure that the labelling of IVDs containing radioactive materials include the information above, all of which can be presented in a clear, language independent fashion.

For instance, a reagent which contains 300 kBq of an antigen labelled with ^{125}I would be labelled:

	**Ag**	**^{125}I** **300 kBq**

Note: that this example has been developed based on current EDMA guidance on the use of symbols.

Labelling Requirements – Secondary labels (IVD Device label as per the IVD Directive)

So as to ensure the safe handling of the IVDs secondary labels (i.e. the kit labels, or label of the outer container) should include at least the radioactivity symbol, the name of the isotope and the amount of radioactivity in becquerels (this can be expressed in an absolute amount e.g. 300 kBq or a relative amount e.g. < 1 MBq). The same labelling conventions can be used as for the primary label.

Labelling requirements – Instructions for use

So as to be in compliance with labelling requirements across the EU the instructions for use (IFU) should contain all of the information on the primary label as well as the following:

1. The nature and intensity of the radiation (alpha, beta, gamma…)
2. The half life of the isotope

This can be expressed in either of two ways:

Ag	**^{125}I** **$t_{1/2}$ = 59.4d**	**300 kBq**
	**γ: 35.5 keV**	**X: 28 keV**

Note that Ag is a symbol for Antigen, whose meaning will need to be explained elsewhere in the IFUs, ideally as a note to this informative table.

Or alternatively:

Contains antigen labelled with 300 kBq of ^{125}I (half-life 59.4 days) emitting γ (35.5 keV) and X (28 keV) ionizing radiation.

Furthermore the information for the means of protecting the user and on ways of avoiding misuse and eliminating the risks inhering in installation must be supplied. That information should be based on the risk analysis of the manufacturer and the details of its exact nature are outside the scope of this document.

References:

Directive 98/79/EC on *in vitro* diagnostic medical devices

Directive 96/29/Euratom on laying down basic safety standards for the protection of the health workers and the general public against the dangers arising from ionizing radiation

The EDMA Labelling Task Force

Annex: Legal Requirements for labelling under the various pertinent directives.

Directive 98/79/EC on in vitro diagnostic medical devices

Recital 13

Whereas this Directive should include requirements regarding the design and manufacture of devices emitting ionizing radiation; whereas this Directive does not affect the application of Council Directive 96/29/Euratom of 13 May 1996 laying down basic safety standards for the protection of the health of workers and the general public against the dangers arising from ionising radiation.

Annex I (Essential requirements) section B 5

5. Protection against radiation

5.1 Devices shall be designed, manufactured and packaged in such a way that exposure of users and other persons to the emitted radiation is minimised.

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 that the characteristics and the quantity of radiation emitted can be controlled and/or adjusted,
- fitted with visual displays and/or audiable warnings of such emissions.

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.

Directive 96/29/Euratom laying down basic safety standards for the protection of the health of workers and the general public against the dangers arising from ionizing radiation

It should be noted that Directive 96/29/Euratom does not contain any specific labelling requirements. Further it does not include IVDs in the list of applications which require prior authorization before use.

However – it is possible that IVDs would fall under Article 3 (reporting requirements). Perhaps because of this many member states in their transpositions have added requirements for the authorization and labelling of IVDs in national transpositions of Directive 96/29/Euratom.