edma DIAGNOSTICS FOR HEALTH

Position Paper

WARNINGS ON CHEMICAL HAZARDS

CLP – THE EU IMPLEMENTATION OF GHS

Impact on the IVD industry

16 April 2014

Introduction

In this document EDMA makes recommendations to in vitro diagnostic medical device (IVD) manufacturers to address a number of issues with regard to device label adaptation which arise over the implementation of the Global Harmonised System for Labelling and Classification of Hazardous Chemicals (GHS). It has been prepared on the assumption that most IVD manufacturers place on the market preparations (mixtures) rather than substances.

IVDs are specifically exempted[1] from the scope of the Regulation 1272/2008 on Classification, Labelling and Packaging of substances and mixtures (CLP Regulation) in order to allow the use of GHS through the specific provisions applicable to IVD labels which are outlined in the IVD Directive 98/79/EC. The current labelling regime of hazardous substances and preparations in IVDs is defined by Directive 67/548/EEC and Directive 88/379/EEC (repealed by directive 1999/45/EC).

Despite this explicit exemption, the CLP Regulation does have an impact on IVD manufacturers. It has amended certain key provisions in both of these directives with effect from 20 January 2009 and will furthermore fully repeal and replace them with effect from 1 June 2015. IVDs are operating in a legal void which could be detrimental to business and confusing for regulators. This issue is expected to be addressed under the future revision of the IVD Directive which will provide the legal basis for use of the CLP Regulation.

Although there is currently no legal requirement for IVD manufacturers to comply with CLP, EDMA makes recommendations to its members on where and how it may be appropriate for them to adopt provisions under CLP with regard to device label adaptation information to be included in the information accompanying the product, notification to the European Chemical Agency (ECHA) classification and labelling inventory, and harmonised classification and calculation rules.

Labelling of Hazardous Substances for IVDs: considerations on the current regime

Under the existing regulatory framework, the following provisions of the IVD Directive apply (see paragraph 8.3[2] of section B of Annex I of the IVDD):

- Danger symbols and labelling requirements of Directive 67/548/EEC and Directive 88/379/EEC: these directives constitute the current legal regime for IVDs with respect to the labelling of hazardous chemicals. Directive 67/548/EEC

[1] CLP Regulation 1272/2008/EU, Article 5(d)

[2] IVD Directive 98/79/EC Annex I, B.8.3.
"In the case of devices containing 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 (2) and Directive 88/379/EEC (3) shall apply. Where there is insufficient space to put all the 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 the aforementioned Directives on the safety data sheet shall apply, unless all relevant information as appropriate is already made available by the instructions for use."

is directly called out by the CLP Regulation, but it must also be noted that Directive 88/379/EEC has been repealed by Directive 1999/45/EC (which will be itself repealed by the CLP Regulation, just like Directive 67/548/EC). Therefore, both references to Directive 67/548/EEC and to Directive 1999/45/EC in the CLP Regulation are of interest to IVDs manufacturers.

- Position of danger symbols and labelling requirements: the IVD Directive requires that "... as far as practicable and appropriate, the information needed to use the device 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."[3] At a minimum danger symbols must therefore be placed on the device itself, while all other information may be placed in the information accompanying the product (for example if full labelling is not practicable due to small device size).

CLP Regulation and hazardous substances: overview of changes and issues

The implementation of the CLP Regulation in the EU will be staggered, with full effects from 1 June 2015 on. Different transition periods are laid down for hazardous substances and hazardous mixtures. Key dates (for mixtures only) include:

- From 20 January 2009 to 1 June 2015: classification, labelling and packaging of mixtures according to Directive 1999/45/EC.
- Possibility to apply CLP Regulation to mixtures as from 20 January 2009. In that case, Directive 1999/45/EC does not apply anymore.
- As from 1 June 2015: full implementation of CLP Regulation (derogations are possible, depending on the date of the placing on the market).

A detailed timeline for the implementation is included in Annex IV of this paper.

Overview of changes introduced by the CLP Regulation

The CLP Regulation introduces several changes to the classification, labelling and packaging requirements laid down in the dangerous chemicals directives. Annex I provides more details on the meaning and extent of these changes:

- New terminology (see Annex II for more details);
- Increased total number of hazard classes and differentiations;
- New calculation methods for the classification of mixtures;
- Supplemental labelling elements: type of information to be included on the label, and coding (see Annex III for more details);
- Harmonised classification: according to the effects, and larger number of actors for a proposal;
- Safety Data Sheets: provisions on information to be provided regarding classification, with staggered implementation.
- Notification of the classification and labelling to the Classification and Labelling Inventory.

[3] See IVD Directive 98/79/EC, Annex I, Essential Requirements, 8.1

Issues with the CLP Regulation

Two major issues must be addressed with regards to the CLP Regulation.

- **Applicable labelling regime for IVDs**

The current labelling regime of hazardous substances and preparations in IVDs is defined by Directive 67/548/EEC and Directive 88/379/EEC (repealed by directive 1999/45/EC).

The CLP Regulation will repeal and replace both Directives 67/548/EEC and 1999/45/EC, with effect from 1 June 2015. Therefore, the current labelling regime of hazardous substances and preparations in IVDs will no longer be valid and applicable.

Once the CLP Regulation enters into force and both directives on the labelling of hazardous chemicals are repealed, references to Directives 67/548/EEC and 88/379/EEC within the IVDD should be read as references to the CLP Regulation[4].

As the CLP Regulation also amends the dangerous chemicals directives (with effect upon the entry into force of the directive on 20 January 2009), the validity and applicability of these directives may become an issue before their actual repeal. Some amendments have important consequences: for instance, annex I concerning classification was deleted from Directive 67/548/EEC which means in practice that the provisions of classification under the CLP are the only ones within the EU Regulatory framework today. Further amendments to the dangerous chemicals directives result in some of the labelling and packaging requirements of CLP being applicable today.

The legal basis for use of the CLP Regulation by IVD manufacturers is expected to be established in the future by the revision of the IVD Directive. The text for an IVD Regulation proposed by the European Commission (2012/0267 (COD)) explicitly refers to the CLP Regulation. The recommendations made by EDMA to the IVD sector in this document are fully in line with the Commission proposal.

As the CLP Regulation excludes IVDs from its scope, manufacturers would not actually be covered by a valid, applicable labelling regime for hazardous substances and preparations in IVDs until the implementation of a new IVD Regulation.

- **Laboratory reagents and Research Use Only products**

Difficulties may also arise from the difference in labelling requirements for substances and preparations in IVD medical devices as defined by Directive 98/79/EC (finished, CE-marked products) on the one hand, and laboratory reagents and Research Use Only products on the other hand, even though these products involve the same degree of risk. Although IVDs are exempted from the CLP Regulation, laboratory reagents and Research Use Only products are not, as they fulfil the definition of substances and mixtures (article 2) and are in no way excluded from the scope (article 1).

However, for laboratory reagents and Research Use Only products under 125 ml in volume, specific and simplified provisions are applicable as defined under section 1.5.2 of Annex I for the CLP Directive.

[4] This is the practice with references in legal texts. For instance, if legislative instrument X repeals legislative instrument Y, then references to legislative instrument Y in legislative instrument Z shall constitute references to legislative instrument X after legislative instrument Y has been repealed

Actions for manufacturers: EDMA's recommendations

Under the CLP regulation, all of the information concerning the hazardous use of a substance needs to be included in the label of the product (with a particular provision for the case of small vials).

Label adaptation

- **Label of the product**

According to the IVD Directive (Annex I, B.8.3), only the relevant danger symbols, as defined by the dangerous chemicals directives must appear on the label of the product. Note that many CLP Regulation hazard pictograms are similar but not identical to the danger symbols currently used by the IVD sector.

The ECHA guidance on the CLP regulation provides useful additional indications on label sizes; locations etc. (see References).

- **Information to be included in the information accompanying the device**

The rest of the information requested under the CLP Regulation (signal words, product identifiers; name, address and telephone number of the supplier; nominal quantity of substance or mixture in the package; additional hazard information…) is not legally required to appear on the label of the product. Rather, it may be included in the information accompanying the device.

- **Other aspects of labelling**

SDS will have to be modified, as the CLP Regulation amends the provisions of the REACH Regulation:

- Substances: the SDS must contain the classification according to both Directive 67/548/EEC and the CLP Regulation from 01/12/2010 to 01/06/2015;
- Mixtures: if mixtures are classified and labelled according to the CLP Regulation before the 01 June 2015 deadline, then the classification shall be provided in the SDS (together with the classification according to Directive 1999/45/EC).

Annex III provides a recap of the labelling requirements with regard to labelling and the IFU.

Classification

- **Notification to the C&L Inventory**[5]

The purpose of notification of classification to the Inventory is to ensure that a harmonised classification of all substances and preparations is maintained.

Notification of the classification and labelling of substances to the Classification and Labelling Inventory established by ECHA is a requirement of the CLP Regulation. These provisions were transferred from the REACH Regulation (formerly Title XI) to the CLP Regulation. Substances and mixtures in their finished state, intended for the final user (i.e. CE-marked IVD medical devices) are exempted from the scope of the Regulation, therefore the notification requirements do not apply to them. They will apply, however, to imported semi-finished products. It should be noted that classification is also relevant for the correct preparation of a registration for the purposes of REACH.

[5] Notification to the C&L Inventory (CLP) should not be confused with notification according to article 7.2 of REACH, where from 2011 EU and EEA producers or importers of articles have to notify ECHA if their article contains a substance on the Candidate List of SVHC (this obligation applies if the substance is present in those articles in quantities totaling over one ton per producer or importer per year and if the substance is present in those articles above a concentration of 0.1% (w/w))

There is therefore no formal requirement for manufacturers of IVDs to comply with the requirements of notification to the inventory of the classification of a substance or preparation which is CE marked and intended for the final user (for other dangerous substances it is obligatory to notify), however it may be appropriate to do so either in regards with the registration procedure under REACH or to ensure that key products are classified in a harmonised way across the EU.

- **Harmonised classification and calculation rules**

The CLP Regulation deletes Annex I of Directive 67/548/EC (harmonised classification). It also takes over this Annex, and includes it in table 3.2 of part 3 of Annex VI of the CLP Regulation (Generic Concentration Limits that appeared in Annex I of Directive 67/548/EC have not been transferred to table 3.2). Table 3.2 of part 3 of Annex VI has been translated (i.e. converted) into corresponding CLP classifications, listed in table 3.1 of Annex VI of the CLP Regulation. Some changes have been made through this translation process:

- In the case of physical hazards, the translations have been made on a re-evaluation of available data.
- With regards to health and environmental hazards, the translations were done by use of a translation table. Where Directive 67/548/EC and the CLP Regulation criteria for classification did not match sufficiently, a minimum classification has been assigned.

Table 3.1 includes also specific concentration limits and a "multiplying factor" to give more weight to substances that are toxic for the aquatic environment when classifying mixtures containing these substances.

IVD manufacturers should compare tables 3.2 and 3.1 of part 3 of Annex VI and verify if any changes will apply to the classification of the substances they currently use. They should also consider any substances or mixtures that are currently not dangerous under Directive 67/548/EC and Directive 1999/45/EC, as under the CLP regulation, some previously non-dangerous substances or mixtures may be classified as hazardous. Particular attention should be given to those preparations known to be on the edge of the classification cut-offs.

Rationale for EDMA recommendations

It is the view of EDMA that a solid case can be made in favour of the label change advocated, which may have a significant impact on manufacturers:

Directive 67/548/EEC and Directive 88/379/EEC will no longer be valid and applicable once repealed by the CLP Regulation. Therefore, manufacturers of IVDs will actually fall in a legal void which will be detrimental to business. Liability cases involving IVD manufacturers may also become more complicated if no valid legal framework applies to them.

Difficulties are to be expected at customs points and for transportation if labelling requirements under the CLP Regulation are not complied with, because authorities will adapt to the new legislative framework and may be reluctant to allow products bearing different labels to clear customs.

Exemptions from the CLP Regulation are limited, and a significant number of suppliers of substances and mixtures to IVD manufacturers are bound to shift to the CLP regime. Communication will be easier throughout the supply chain if there is some form of harmonisation on classification, labelling and packaging.

The CLP Regulation has been designed to work in conjunction with the REACH Regulation. It amends for example some of the provisions on safety data sheets (e.g., it requests SDS for substances to contain the classification according to Directive 67/548/EEC and the CLP Regulation from 1 December 2010 until 1 June 2015). IVD

manufacturers are covered by REACH. Therefore, the combination of these two legislative instruments may be easier if some aspects of the CLP Regulation are complied with by industry.

Other countries will implement the GHS. Therefore, it is the view of EDMA that the GHS (and its corresponding European text, the CLP Regulation) represents one step closer to the internationally harmonised label that EDMA and manufacturers are striving for.

The legal conundrum created by the implementation of the CLP Regulation is one of the issues that EDMA wishes to address during the revision of the IVD Directive. However, this process won't be completed before the next couple of years; manufacturers must be able to operate under a clear legal framework before.

As explained above, IVD manufacturers are already in practice implementing some of the provisions of the CLP Regulation (classification), due the changes introduced by the Regulation to the dangerous chemicals directives.

European and international aspects of the GHS

ECHA is in charge of providing industry with technical and scientific guidance and tools on how to comply with the obligations of the CLP Regulation. In this perspective, ECHA has published on 28 August 2009 guidance on the CLP Regulation and guidance on the application of the CLP criteria which can be consulted on the ECHA website.

As the GHS originates at the level of the UN, it is a system which is expected to have global implementation in the coming years. Indeed, every single major country has a GHS implementation policy which is either established or under development, including important field players in the IVD sector (USA, Japan, Australia, China, Brazil, South Africa, etc.). More than 67 different countries are reported as having a GHS implementation programme.

About EDMA

Committed to raising awareness of the important role of diagnostics in the entire healthcare equation, the European Diagnostic Manufacturers Association (EDMA) provides services and activities to members engaged in the research, development, manufacturing or distribution of in vitro diagnostic (IVD) products in Europe. Founded in 1979, EDMA advocates for an appropriate regulatory system and a realistic economic environment for healthcare in Europe.

For more information visit www.edma-ivd.eu.

References:

- Directive 98/79/EC on In Vitro Diagnostic Medical Devices (IVD Directive)
http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:31998L0079:en:NOT

- Proposal for a Regulation on In Vitro Diagnostic Medical Devices - COM(2012) 541
http://ec.europa.eu/health/medical-devices/files/revision_docs/proposal_2012_541_en.pdf

- Regulation (EC) 1272/2008 on Classification, Labelling and Packaging of substances and mixtures (CLP Regulation)
http://eur-lex.europa.eu/Notice.do?val=486098:cs&lang=en&list=555563:cs,555564:cs,555566:cs,555559:cs,555561:cs,490877:cs,486098:cs,&pos=7&page=1&nbl=7&pgs=10&hwords=&checktexte=checkbox&visu=#texte

- ECHA summary page on CLP
http://echa.europa.eu/regulations/clp

- ECHA guidance on the CLP regulation
http://echa.europa.eu/documents/10162/13562/clp_en.pdf

- ECHA Questions & Answers on CLP Regulation
http://echa.europa.eu/web/guest/support/faqs/clp-frequently-asked-questions

Annex I – overview of main changes introduced by the CLP Regulation (vs the dangerous chemicals directives and REACH)

	Dangerous chemicals directives / REACH	**CLP Regulation**
(a)	Terminology of Directive 67/548/EC	Terminology of the CLP Regulation
(b)	Categories of danger for physical, health and environmental hazards of Directive 67/548/EC	CLP Regulation hazard classes and their differentiations. Total number of hazard classes higher under the CLP Regulation than total number of categories of danger under Directive 67/548/EC
(c)	Calculation rules ("conventional method") for the classification of preparation of Directive 1999/45/EC	CLP Regulation calculation methods (additivity, summation) deviating from the calculation rules of Directive 1999/45/EC
(d)	Categories of danger and additional labelling elements (e.g. R1 "Explosive when dry) of Directive 67/548/EC	CLP Regulation hazard classes and supplemental labelling elements taken over from Directive 67/548/EC (e.g. EUH001 "Explosive when dry")
(e)	Requirements for Safety Data sheets laid down in the REACH Regulation (art.31 and Annex II)	The CLP Regulation amends REACH and provides for new requirements regarding the information to provide regarding classification
(g)	If harmonised classification, then normally for all categories of danger	If harmonised classification, then for substances which carcinogenic, mutagenic, toxic to reproduction or respiratory sensitisers; other effects on a case-by-case basis
(g)	Harmonised classification based on a Member State proposal	Harmonised classification based on a Member State proposal, or a proposal by a manufacturer, importer or downstream user
(h)	List of substances with their harmonised classification and labelling of Annex I of the Directive 67/548/EC	Annex I of Directive 67/548/EC deleted and replaced by part 3 of Annex VI of the CLP Regulation
(i)	No notification procedure	Notification of the classification and labelling of substances to the Classification and Labelling Inventory established by ECHA

(a) See Annex II for more details.

(b) The hazard classes are broken down into hazard differentiations which take into account the severity of the effect or the route of exposure. As a result, and whole the overall scope of classification under the CLP Regulation is similar to that of Directive 67/548/EC, the total number of hazard classes has increased, in particular for physical hazards (from 5 to 16).

(c) With regard to health and environmental mixture classification, the calculation rules have changed, in comparison to Directive 1999/45/EC. "Bridging principles" (allowing the classification of mixtures on the basis of data on

similar tested mixtures and information on individual hazardous ingredient substances) have also been introduced as a new approach to classify mixtures.

(d) Some elements currently featuring in the dangerous chemicals directives are not included in the UN GHS (e.g., the EU hazard class “Hazardous to the ozone layer”, or some hazards which have led to additional labelling under Directive 67/548/EC, e.g. “R1 – Explosive when dry”). These elements are retained as supplemental labelling information, and can be found in Part 5 of Annex I, and in Annex II, of the CLP Regulation. In order to make clear that these supplemental labelling elements do not stem from a UN classification, they are coded differently from the CLP Regulation hazard statements (e.g. the additional labelling R1 – “Explosive when dry” of Directive 67/548/EC becomes EUH001 instead of H001 in the CLP Regulation).

(e) For more information, please see EDMA Labelling News 4 on Safety Data Sheets.

(f) With regard to harmonisation of classification and labelling of substances at Community level, the CLP Regulation lays down the harmonised classification of substances which are carcinogenic, mutagenic or toxic to reproduction, and of respiratory sensitisers category 1.

(g) Proposals relating to other hazard classes may be submitted on a case-by-case basis where justification may be submitted by manufacturers, importers and downstream users (this was not the case with the dangerous chemicals directives).

(h) Article 55 of the CLP Regulation amends Directive 67/548/EC. Article 55(11) deletes Annex I of the directive. The CLP Regulation takes over Annex I of the directive and includes it in table 3.2 of part 3 of Annex VI of the CLP Regulation (Generic Concentration Limits that appeared in Annex I of Directive 67/548/EC have not been transferred to table 3.2 of Annex VI of the CLP Regulation). Table 3.2 of part 3 of Annex VI has been translated (i.e. converted) into corresponding CLP classifications listed in table 3.1 of Annex VI of the CLP Regulation, with some changes (in the case of physical hazards, the translations have been made on a re-evaluation of available data. With regards to health and environmental hazards, the translations were done by use of a translation table included in Annex VII to the CLP Regulation. Where Directive 67/548/EC and the CLP Regulation criteria for classification did not match sufficiently, a minimum classification has been assigned).

An additional change has been made to table 3.1, vs table 3.2: table 3.1 includes specific concentration limits and a “multiplying factor” (“M-factor”) to give an increased weight to substances that are very toxic for the environment when classifying mixtures containing these substances.

Until 31 May 2015, new entries to the tables of harmonised classification are made both in table 3.2 and in table 3.1. After this date, only table 3.1 will be updated.

(i) The CLP Regulation provides for the new obligation to notify the classification and labelling of substances placed on the market to a database established and maintained by ECHA (the European chemicals Agency): “the Classification & Labelling Inventory”. The provisions on notification to the Inventory at ECHA were transferred from the REACH Regulation (Title XI) to the CLP Regulation.

Annex II – Changes in the terminology

Dangerous chemicals directives	**CLP Regulation**
MSDS (Material Safety Data Sheets)	SDS (Safety Data Sheet)
Category of danger	Hazard class
Preparation	Mixture
Symbol	Hazard pictogram
Risk phrase	Hazard statement
Safety phrase	Precautionary Statement
	Signal word (new)

Example:

Label elements for flammable gases

Classification	Category 1	Category 2
GHS Pictogram		No pictogram
Signal Word	Danger	Warning
Hazard Statement	H220: Extremely flammable gas	H221: Flammable gas
Precautionary Statement Prevention	P210	P210
Precautionary Statement Response	P377 P381	P377 P381
Precautionary Statement Storage	P403	P403
Precautionary Statement Disposal		

Annex III – Implementation of the CLP Regulation regarding labelling of substances or mixtures classified as hazardous:

		Location	
Comment number	**Labelling information**	**Product label**	**Information accompanying the device**
	Name, address, telephone number of the supplier(s)		X
	Nominal quantity of the substance or mixture		X
(a)	Product identifier		X
(b)	Hazard pictogram	X	X
(c)	Signal word		X
(d)	Hazard statement		X
(e)	Precautionary statement		X
(f)	Supplemental information		X

(a) Product identifiers: covered by the IVD Directive.

(b) Rules of precedence are laid down in the CLP Regulation where the classification of a substance or mixture would result in more than one pictogram on the label.

(c) Signal words (“danger” or “warning”) are new requirements of the CLP Regulation. Only one signal word appears on the label. The signal word is determined by the classification of the hazardous substance or mixture (see parts 2 to 5 of Annex I of the CLP Regulation).

(d) Full hazard statements with its reference number (for example, “H314: Causes severe skin burns and eye damage”) should be provided in the IFU.

(e) Full precautionary statements with its reference number (for example, “P102 – Keep out of reach of children”) should be provided in the information accompanying the product.

(f) Supplemental information: supplementary statements can be included in the IFU where a substance or mixture classified as hazardous has certain physical or health properties. If the substance is included in part 3 of Annex VI, any supplemental hazard statement given therein for the substance must be included in the supplemental information in the label (for IVD manufacturers, in the information accompanying the product).

Annex IV – timeline for the implementation of the CLP Regulation

<table>
<tr><th></th><th>2009</th><th>2010</th><th>2011</th><th>2012</th><th>2013</th><th>2014</th><th>2015</th></tr>
<tr><td rowspan="2">Substances</td><td colspan="2">Classification, labelling and packaging acc. to dir. 67/548/EC.</td><td colspan="4" rowspan="2">Classification both acc. to dir. 67.548.EC and CLP reg.
Labelling and packaging acc. to CLP reg.</td><td rowspan="3">Classification, labelling and packaging acc. to CLP reg.</td></tr>
<tr><td colspan="2">By way of derogation, CLP reg. can already be applied in full.
In that case, dir. 67/548/EC does not apply for labelling and packaging</td></tr>
<tr><td rowspan="2">Mixtures</td><td colspan="6">Classification, labelling and packaging acc. to dir. 1999/45/EC.</td></tr>
<tr><td colspan="6">By way of derogation, CLP reg. can already be applied in full.
In that case, dir. 1999/45/EC does not apply for labelling and packaging.</td></tr>
</table>

20/01/2009
CLP into force

01/12/2010
Obligation to apply CLP reg. to substances

Possible derogation until 01/12/2012 for re-labelling and repackaging of certain substances

01/06/2015
Obligation to apply CLP reg. to mixtures and substances (includes most IVD reagents)

Possible derogation until 01/12/2017 for re-labelling and repackaging of certain mixtures