UNDERSTANDING THE EC DIRECTIVE 98/79/EC ON IN VITRO DIAGNOSTIC MEDICAL DEVICES

A WHITE PAPER ON THE REQUIREMENTS, REGULATIONS AND OPPORTUNITIES CONTAINED IN EC DIRECTIVE 98/79/EC AND A BRIEF COMPARISON TO OTHER GLOBAL REGULATORY SCHEMES FOR IVD MEDICAL DEVICES

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ABSTRACT

The purpose of this white paper is to provide an introduction to the European Union’s EC Directive 98/79/EC on in vitro diagnostic medical devices (IVDs). This document is not intended to provide every possible detail on the European regulatory requirements for IVDs or their implementation, due to the level of complexity involved. Instead it aims to advance understanding of the key requirements that manufacturers of IVDs need to comply with in order to sell their products in Europe, and briefly compares European regulations with the medical device regulatory frameworks of the United States, Canada and Japan.

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I. EXECUTIVE SUMMARY

Even with an increasing move toward global harmonisation between the major medical device regulatory schemes of Europe, North America and Asia, there is still a need for a detailed understanding of these regional schemes, especially for those responsible for product compliance with regulatory affairs.

The European Union’s regulatory scheme for IVD medical devices (EC Directive 98/79/EC on IVDs)¹ has been in place as a mandatory legal requirement since 2003, with the EU’s product conformity marking (CE Marking) now permitting regulatory access to the 30 European nations that make up the European Economic Area (EEA) and Switzerland, a significant market region. EC Directive 98/79/EC (hereafter abbreviated as 98/79/EC) represents a robust and workable regulatory framework based on ISO 13485 for quality system compliance. This can integrate into a manufacturer’s existing system and processes to meet the additional regulatory requirements and ensure device compliance.

IVD manufacturers need the knowledge to make decisions on the conformity route they take to comply with 98/79/EC and, where necessary, the choice of the regulatory third party, the Notified Body that they work with to successfully navigate that process.

II. REGULATORY CHALLENGE FOR IVD DEVICE MANUFACTURERS

The global market for IVDs is, unsurprisingly, an extremely regulated one. Safety for users and end users (the patient) of IVDs is of critical importance, which includes acceptable clinical performance for the intended use. The challenge for IVD manufacturers is to understand the complex array of regulations for the markets they sell into and how it applies to their specific products. By doing this, they can ensure that their products are compliant for efficient entry into that market and to remain on the market, maximising their commercial potential. Knowledge of the similarities and, sometimes even more importantly, the differences between global regions is crucial to meet regulatory requirements efficiently.

Within Europe, the responsibility for ensuring the safety and health of the population with regard to IVD devices resides with individual EU member state governments, but is legally transposed from 98/79/EC and is implemented by each national Competent Authority¹. In order to maintain a consistent level of safety and performance throughout the region, these regulations apply to any IVD placed on the European market, regardless of where it was manufactured. Compliance with the provisions of 98/79/EC is demonstrated by the CE Marking displayed on the device, allowing free movement of the product within the region. The current extent of this European market includes the EU member states (27 at present) as well as those additional members of the European Economic Area (EEA) and Switzerland. Further EU candidate countries are expected to join in the future.

EC DIRECTIVE 98/79/EC – HISTORICAL TIMELINE

The stated aim of the European Commission in enacting 98/79/EC was, “To ensure the highest level of patient safety while promoting the innovation and the competitiveness of this sector, allowing for market access, international trade and regulatory convergence.”

1957
Treaty of Rome establishes the European Economic Community (EEC).

1985
Council of the European Communities Resolution on New Approach to Technical Harmonisation and standards.¹

1990
Council of the European Communities Directive on active implantable medical devices (AIMD) 90/385/EEC.

1993
Council of the European Communities Directive on Medical Devices (MDD) 93/42/EEC.

1993
European Union (EU) established by the Treaty of Maastricht, an economic and political union of member states, replacing and built upon the foundations of the EEC.

1994
Agreement on European Economic Area (EEA), which includes three of the four members of the European Free Trade Association (EFTA) – Norway, Iceland and Liechtenstein – and brings them into the EU Internal Market.

1998
Council of the European Union Directive on In Vitro Diagnostic medical devices 98/79/EC.

1999
Switzerland (fourth EFTA member) completes bilateral agreements with the EU across a wide range of areas, including movement of persons, transport and technical barriers to trade.

2003
ISO 13485 issued as a quality management system standard for medical device and IVD manufacturers and is recognised as a harmonised standard for the Medical Device Directives.

2007
Council of the European Union Directive 2007/47/EC, technical revision to AIMD and MDD.

2008
European Commission consults with stakeholders on the revision of the legal framework for medical devices – a “recast” of all three Directives.²

SCOPE AND LEGAL DEFINITIONS

The scope of 98/79/EC applies to IVD medical devices and accessories, which can include not just reagents and kits but also instruments and software. Article 1 of 98/79/EC gives the legal definitions which confirm that IVDs are a specific category of medical devices with particular differences and are therefore controlled under this separate Directive. It builds upon the basic medical device definition to state that:

- “An IVD medical device is 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.”

This also includes specimen receptacles, but general laboratory equipment is excluded. The first step for any manufacturer is to determine that their device actually falls under the above definition, with a clear medical purpose.

ESSENTIAL REQUIREMENTS (ER) AND HARMONISED STANDARDS

98/79/EC, because it has to apply to the whole spectrum of IVDs, does not define specific technical factors but instead identifies broad based essential safety requirements to be met by all devices. More detailed technical solutions to compliance are given by the specifically developed or adopted European harmonised standards, which give a “presumption of conformity” to particular areas of the Essential Requirements (ER) in Annex I of the Directive. ISO 13485 is recognised as the harmonised standard for regulatory quality system compliance, and all such standards are published in the EU’s Official Journal.
CLASSIFICATION
The risk presented by a device determines the classification, and therefore the level of control and regulatory review required. Annex II of the Directive identifies specific device types that are categorised as either high risk (List A) or moderate risk (List B), so only the particular devices meeting that description are classified as such, for example only reagents for the tumour marker PSA are List B but no other equivalent cancer marker.
Self-test IVDs, because of the greater risk associated with being used by untrained lay users, have special requirements while all other devices not classified as either List A, List B or self-test are regarded as general IVDs.

TECHNICAL DOCUMENTATION AND PERFORMANCE EVALUATION
A key obligation is for all IVDs to have Technical Documentation, as described in Annex III, to provide the supporting evidence for their compliance with the Essential Requirements. Central to this documentation will be the performance evaluation of the device, demonstrating that the performance meets the claims and intended use specified by the manufacturer. For List A devices the Common Technical Specification (CTS) give the criteria for the expected “state-of-the-art” performance evaluation.

CONFORMITY ASSESSMENT ROUTES AND NOTIFIED BODY ROLE
As a New Approach Directive, 98/79/EC aims to give manufacturers different options to reach conformity with the requirements. These different conformity routes are dependent on the classification of the device and hence are linked to the perceived risk of that product.
Under the EU’s regulatory scheme, each national Competent Authority has responsibility for the implementation of the Directive in their country, but pre-market approval is delegated to specifically designated independent third parties called Notified Bodies. For higher risk devices (List A, List B and Self-Test) this means that the manufacturer must gain independent certification by a Notified Body in order to complete the conformity route process, apply for CE Marking and be able to place the device on the European market.
For the very highest risk devices in List A, there are additional measures required to address this high risk. Under the Full QA conformity route of Annex IV, each List A device must undergo a detailed review of the technical documentation called the EC Design Examination. Once approved for CE Marking, by either of the permitted routes, every batch of List A product has on-going batch verification before it is released into the market to ensure the continued consistent performance of the device.
<table>
<thead>
<tr>
<th>CLASS OF IVD</th>
<th>AVAILABLE CONFORMITY ROUTES</th>
<th>TYPE OF ROUTE</th>
<th>ADDITIONAL REQUIREMENTS AS PER ROUTE</th>
<th>NOTIFIED BODY REQUIRED</th>
</tr>
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<tbody>
<tr>
<td><strong>LIST A</strong></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Annex IV</td>
<td>Full quality assurance (QMS - design and manufacturing)</td>
<td>EC Design Examination + Batch Verification</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Annex V and Annex VII</td>
<td>EC Type Examination (product testing) and Production quality assurance (QMS - manufacturing)</td>
<td>+ Batch Verification</td>
<td>Yes</td>
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<tr>
<td><strong>LIST B</strong></td>
<td></td>
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<tr>
<td></td>
<td>Annex IV</td>
<td>Full quality assurance (QMS - design and manufacturing)</td>
<td>n/a</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Annex V and Annex VII</td>
<td>EC Type Examination (product testing) and Production quality assurance (QMS - manufacturing)</td>
<td>n/a</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Annex V and Annex VI</td>
<td>EC Type Examination (product testing) and EC Statistical Verification (product testing)</td>
<td>n/a</td>
<td>Yes</td>
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<tr>
<td><strong>SELF-TEST IVDs</strong></td>
<td></td>
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<td></td>
<td>Same as for List B plus:</td>
<td></td>
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<tr>
<td></td>
<td>Annex III section 6</td>
<td>EC Design examination for self-test products only</td>
<td>n/a</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>GENERAL IVDs</strong></td>
<td></td>
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<td></td>
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<tr>
<td></td>
<td>Annex III</td>
<td>EC Declaration of Conformity (self declaration by manufacturer)</td>
<td>n/a</td>
<td>No</td>
</tr>
</tbody>
</table>
REGISTRATION AND AUTHORISED REPRESENTATIVES

A remit for a European databank to share critical data between competent authorities is described in 98/79/EC, but currently the project is still underway. When in place, it will mean that only a single registration in the manufacturer’s home country or where their Authorised Representative (AR) is located is necessary, but in the meanwhile an interim situation requires that initial registration but then also a notification to other member state’s competent authorities. Manufacturers need to research the specific implementation requirements for each member state to confirm if they require notification if they are a potential market country.

Non-EU manufacturers need only one AR within the EU region, to act on their behalf and be a legal contact point, but they need to ensure they have a suitable agreement or contract with the AR that clearly defines the AR’s duties.

LABELLING AND CE MARKING

Essential Requirements (ER 8.1 – 8.7) define the type and minimum content of information to be provided to the user, where the labelling includes both the labels and Instructions for Use (IFU) of the device. This includes clearly identifying the legal manufacturer and the intended use of the IVD device.

Additional criteria apply to self-test devices, focussing on the clarity of the information for non-professional users. There are national language requirements for labelling, which are obviously mandatory for self-test IVDs where the user has to have instructions in their own language but there may be some flexibility regarding professional use devices on acceptable alternative languages, such as English. Manufacturers need to research for each member state it plans to sell their product in, to ensure they are compliant.

The IVD manufacturer is responsible for any translations and must treat outsourced translation services as subcontracting and control it appropriately.

CE Marking, in the correct format defined in Annex X, is displayed on labelling along with details of an AR if one is involved, and allows free movement of the device throughout the EU, the EEA and Switzerland.

VIGILANCE & POST-MARKET SURVEILLANCE

While Notified Bodies are involved in the pre-market approval process, the Competent Authorities (CA) concentrate on post market surveillance. Manufacturers are required to set up an ongoing systematic process to review experience gained for their device on the market and to have a vigilance procedure to immediately inform relevant Competent Authorities of incidents involving their device (98/79/EC article 11). This is a critical area and European Commission guidance for manufacturers is available¹, which was last updated in 2009.

Each member state CA still has the ultimate power to invoke the safeguard clause (98/79/EC article 8) to remove a device that they believe is unsafe from their national market.

1. MEDDEV 2.12/1 rev.6 on medical device vigilance system, dated Dec 2009.
The technology and prevalence of IVDs has changed over the years, and the corresponding regulations to control these products have also developed with ever more regions worldwide defining their own regulations for IVDs. 98/79/EC has many concepts in common with other key global regulatory systems such as: classification based on device risk; pre-market approval; basic safety criteria; QMS requirements (often based on ISO 13485); post market surveillance; and risk management throughout the life of the device.

However, it is the differences in the specific details between these schemes that require particular attention. The first key area is consideration of the actual definition of an IVD product. Under US, Canadian and Japanese regulations, IVDs are just considered to be types of medical devices and come under their general medical device regulations, compared to the specific regulation of the IVD Directive. Under 98/79/EC, device classification is determined by a listing system of individual device types while Canada uses a rule based classification and in US and Japan there are defined product categories, so the same device may not have the same classification in each region as the method of determining it varies. Future developments of 98/79/EC will most likely see a change to a rule based classification for IVDs, in line with the Global Harmonisation Task Force (GHTF) guidance, and general medical devices under the Medical Devices Directive 93/42/EEC.

The responsibilities of the national Competent Authorities in each EU country as well as the role and remit of the Notified Bodies is clearly defined in the 98/79/EC. In practice this can allow a faster and more predictable pre-market approval route, when compared to certain other global regulatory schemes, which benefits the manufacturer. In other regions the proportion of involvement of third party “Conformity Assessment Bodies” (CAB) varies, from quality system assessment by Accredited Persons in the US and Recognised Registrars in Canada, to technical documentation review for moderate risk devices by Registered Certification Bodies in Japan.

<table>
<thead>
<tr>
<th>REGULATORY AUTHORITY</th>
<th>EU</th>
<th>USA</th>
<th>CANADA</th>
<th>JAPAN</th>
</tr>
</thead>
<tbody>
<tr>
<td>REGULATORY SCHEME</td>
<td>98/79/EC (IVDs only)</td>
<td>Code of Federal Regulations Title 21 (21CFR) (medical devices and IVDs)</td>
<td>Canadian Medical Device Regulations (MDR) (medical devices and IVDs)</td>
<td>Japanese Pharmaceutical Affairs Law (PMDAL) (medical devices and IVDs)</td>
</tr>
<tr>
<td>CONFORMITY ASSESSMENT FOR PRE-MARKET APPROVAL</td>
<td>3rd Party Notified Bodies for high and moderate risk devices Registration with CA only for low risk devices</td>
<td>FDA process: pre-market approval (PMA) for high risk, 510(k) and exemption for some low risk devices Site inspection by FDA or 3rd Party under Accredited Persons Program for Quality System Requirements (QSR)</td>
<td>Health Canada pre-market approval of technical documentation 3rd Party Recognised Registrar ISO 13485 certification under CMDCAS (Canadian Medical Device Conformity Assessment Scheme) for II, III and IV only</td>
<td>Pharmaceutical and Medical Devices Agency (PMDA) approval for high risk products 3rd Party Registered Certification Body (RCB) assessment of moderate risk devices Notification of low risk devices with PMDA</td>
</tr>
</tbody>
</table>

* GMDN - Global Medical Device Nomenclature system (http://www.gmdnagency.org/).
V. CONCLUSION

98/79/EC is a good example of state-of-the-art regulation, aiming to keep pace with product innovation and new clinical knowledge, and with future changes and improvements as part of a defined programme. It has harmonised regulatory requirements and allows for the free movement of goods across a large economic region of in Europe, giving clear responsibilities to manufacturers and the key entities within the regulatory framework (Notified Bodies and National Competent Authorities) with the ultimate aim of patient safety.

The use of designated and monitored Third Party Notified Bodies permits the manufacturer choice and transparency in the regulatory process, allowing them to contract with a Notified Body they feel most compatible with and who is focussed on service delivery. In the wider global regulatory scene, working with a third party Conformity Assessment Body that is able to deliver regulatory certification and support across the global market regions that the manufacturer needs is critical.
ABOUT THE AUTHOR

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Sharon Williams has over eight years experience working in quality assurance and regulatory affairs roles within the IVD industry sector, and has spent the last ten years working for a UK Notified Body as an IVD Directive Specialist. She is now responsible for the technical development of the SGS’s IVD sector certification services, including ISO 13485 and 98/79/EC, to further enhance the current portfolio of medical device regulatory certification schemes that SGS are recognised for globally.

ABOUT SGS

SGS is the world’s leading inspection, verification, testing and certification company. Recognised as the global benchmark for quality and integrity, we employ over 59,000 people and operate a network of more than 1,000 offices and laboratories around the world. As your partner in medical device certification, SGS helps ensure your medical devices, including IVDs, are safe, legal and that they get to the market in the minimum amount of time and remain in the market allowing you to maximise their market potential. SGS has a global network of qualified medical device and pharmaceutical auditors able to provide auditing and training services from more than 40 countries. This allows SGS to support those customers to meet their regulatory obligations with recognised certification across a range of regulatory schemes that are essential for marketing their products around the world, including North America, the EU and Asia Pacific.

In addition, SGS is a Notified Body under 98/79/EC with an initial scope of designation which includes all LIST B devices and Self-Test IVD devices. This scope will be further expanded to include all List A devices during the latter part of 2010.

FOR MORE INFORMATION, VISIT WWW.SGS.COM/MEDICALDEVICES OR EMAIL MEDICALDEVICES@SGS.COM

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