

WHITE PAPER

IVD DIRECTIVE RECAST - WHAT'S IN STORE?

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Directive 98/79/EC regulates all the activities deemed necessary to ensure safety and performance of an In Vitro Diagnostic (IVD) device sold within the European market. The IVD Directive was published on 7 December 1998 and has been in effect since 7 June 2000. At the end of a five-year transition period on 7 December 2003, compliance with the IVD Directive became mandatory for IVDs prior to their being placed on the European market.



During the years since implementation, several areas for possible revision have been discussed in order to address some perceived weaknesses in the requirements or implementing measures. Among these points for consideration is the potential for a revision of IVD risk categorization. This is because only a very limited number of devices (those listed in Annex II of the IVD Directive and self-testing devices) require more rigorous oversight prior to being CE marked and placed on the market. This White Paper reviews the possible changes that might result from the European Commission's 'recast' process for the IVD Directive.

The IVD industry continues to expand and evolve, from both scientific and technological points of view and for this reason some aspects, such as IVD laboratory services, point of care issues, in-house testing, etc., have now become routine, whereas they were not taken into account during development of the directive.

In addition, a difference in device categorization exists between Europe and other countries, such as the United States (US) where each product is classified into one of three different classes, based on the level of control necessary to assure device safety and effectiveness.

For these reasons, it was considered necessary at a European Community level, to revise the IVD Directive, taking into account some additional horizontal regulatory aspects, already under discussion in the review of other medical devices directives. Such aspects include the designation and monitoring of Notified Bodies,

post-market vigilance, and market surveillance, together with the implementation of the revised cross-sector 'New Approach' legislation.

On 29 June 2010, the European Commission published a Public Consultation on the revision of the IVD Directive, but comments were requested only for specific technical and regulatory aspects of the directive. The comments received from the Public Consultation were published by the European Commission on 23 February 2011, from which it was clear that the proposed revision was welcomed by all stakeholders, including manufacturers, Competent Authorities, Notified Bodies, users, and laboratories.

Some of the main issues expected to be addressed in the subsequent recast of the IVD Directive are:

- Classification

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- Conformity assessment procedure
- Scope
- Clinical evidence
- Other topics

Each of these aspects is discussed briefly in the remainder of this paper.

Classification

It is widely accepted by stakeholders that there is a need to change and improve the categorization of IVDs in the IVD Directive to adopt a risk-based classification system as described in documents published by the Global Harmonization Task Force (GHTF). The GHTF proposal classifies IVDs into four different classes, as indicated in Table 1.

Among the issues raised by some stakeholders regarding classification is the need to have a more detailed risk based classification of IVDs in order to avoid any controversial or inconsistent interpretations of the current categorizations by manufacturers, which could lead to discrepancies in regulatory control of similar products and fragmentation within the internal market.

In contrast, other stakeholders, mostly manufacturers, pointed out that the application of risk based classification could lead to an increase in costs for ensuring compliance with regulatory requirements, especially for manufacturers of Class B and C devices, who will be obliged to involve Notified Bodies in the CE marking process for their devices. This could have a significant impact on small and medium enterprises (SMEs), companies that have no devices currently on the market that require Notified Body involvement, and manufacturers with an extensive portfolio of products. This impact could be mitigated by allowing a sufficient transitional period, perhaps 5 years.

Conformity Assessment procedure

Based on the GHTF system classification, a change of the current conformity assessment would be necessary and 75% of respondents to the Public Consultation agreed with this need. The main suggested changes include:

- Deleting Annex VI (EC verification) or limiting it just to specific products, such as instruments, as this conformity assessment route is rarely used by manufacturers and does not include an assessment of the vigilance system
- Aligning conformity assessment procedures for self-tests to those required for current Annex II List B tests, meaning that manufacturers of self-testing devices should have in force a quality management system (QMS) audited by a Notified Body that will issue an EC certificate (quality system certificate)
- Clarifying the requirements of Annex V (Type examination)

It was also suggested that manufacturers should have a Notified Body certificated QMS for Class B, C and D IVDs. EDMA, the European trade association for manufacturers of IVD devices, and Notified Bodies support the use of EN ISO 13485 for this purpose. This proposed amendment could affect around 80% of the IVDs on the market, because it would require Notified Body involvement for Class B and C devices, whereas manufacturers of Class D devices already need to have a QMS audited by a Notified Body before CE marking their products.

The proposed IVD classes are given in Table 2, together with their corresponding conformity assessment routes.

Table 1: Proposed IVD classification system

Class	Risk Level	Examples
A	Low individual risk and low public health risk	Clinical chemistry analyzers, prepared selective culture media, specimen receptacles.
B	Moderate individual risk and/or low public health risk	Anti-nuclear antibody, pregnancy self-testing, fertility testing, urine strips, vitamins, hormones, enzymes, H. Pylori, specific IgE assays, celiac disease and metabolic markers, blood gasses.
C	High individual risk and/or moderate public health risk	Blood glucose self-testing, pre-natal screening (Rubella or Toxoplasma), infective disease status (Enterovirus, CMV, HSV in transplant patients) or infectious agent (Chlamydia pneumonia, Staphylococcus aureus, Neisseria meningitides), sexually transmitted agents (Chlamydia trachomatis), PSA screening, HLA typing.
D	High individual risk and high public health risk	HIV, HCV, HBV, HTLV, some blood-group typing

There was almost unanimous consensus among stakeholders to implement batch release testing verification by a Notified Body for high risk products, similar to how it is currently performed for products included in Annex II List A. However, there were disagreements on how and by whom this batch release verification should be performed: by an independent laboratory or by the Notified Body directly, or by the manufacturer following procedures previously approved by the Notified Body.

There was general agreement among all participants of the Public Consultation regarding the need to maintain the Common Technical Specifications (CTS) for Class D products, as well as, the fact that it should not be extended to other IVD tests, even though a few respondents were in favor of expanding the CTS to certain Class C devices.

Scope

In-house tests: Most respondents wanted to maintain the exemption for in-house tests as provided for in Article 1(5) of the current IVD Directive. The in-house (or "home brew") tests are those *"devices manufactured and used only within the same health institution and on the premises in the immediate vicinity without having been transferred to another legal entity"*. The rationale for keeping this exemption is that sometimes use of in-house tests can facilitate the detection of diseases for which IVDs are not otherwise available. However, the common opinion is that this exemption in the Directive is too large and should be restricted to specific situations where there is no similar commercially available IVD, or in case of rare disease testing, novel analytes, or customized tests for common genetic diseases.

Genetic tests: It is still ambiguous if and how the scope of the IVD Directive will be extended to

include genetic tests, with both direct and indirect medical purposes, while most of the stakeholders agreed to the introduction of additional requirements (similar to the ones currently applicable for self-test devices) and/or restrictions (some respondents proposed a ban) for direct-to-consumer genetic tests.

Amending the definition of "putting into service":

Diagnostic services: More than 80% of respondents supported the need to amend the "putting into service" definition, wishing to clarify that Directive 98/79/EC should also cover IVDs that are not placed on the market as such, but are used for the delivery of results within the European Community, such as at an economic operator's facility.

What is more, most of the respondents were in favor of introducing specific requirements for tests used for diagnostic services, especially when the results of the tests are provided directly to consumers.

Point of care or near patient devices: An increasing number of devices that are intended for use near the patient in an environment different from laboratories, by professionals, are now present on the market. Some requirements for CE marking these devices are already included in the current directive, but it is a common opinion that current requirements are not sufficient. So there is a proposal to set up specific requirements for point of care or near patient testing, such as the need to ensure provision of the same sensitivity and specificity as the tests performed in a lab.

Clinical evidence

The concept of clinical evidence associated with IVDs is not new, but it is not covered in great detail in the IVD Directive. The performance evaluation of IVDs is based primarily, but not

Table 2: Possible conformity assessment procedures

Class	Conformity assessment procedure	Note
A	Annex III OR Annex V & VII OR Annex IV	QMS in place but certification not required. No Involvement of Notified Bodies
B	Annex III & certified QMS OR Annex V & VII & certified QMS OR Annex IV	QMS system certified by a Notified Body, but no premarket review of the technical documentation
C	Annex IV OR Annex V & VII and certified QMS	Notified Body involvement in the certification of the QMS and in the review of technical documentation.
D	Annex IV	Notified Body involvement in the certification of the QMS and in the review of technical documentation.

exclusively, on analytical studies rather than tests of patient samples to support the product's intended use. This is perhaps the biggest difference between the US and European IVD regulatory systems. The introduction of specific requirements for clinical evidence could be one of the most significant changes in the European regulation of IVDs and manufacturers should pay particular attention to this potential new requirement. At the moment, however, it is not clear which concepts of clinical evidence will be introduced or how clinical evidence should be demonstrated. Despite the need for further clarification and updates, introducing definitions of clinical validity and clinical utility into the directive, thereby clarifying the requirements for clinical evidence, was positively evaluated by most respondents.

Clinical validity: "Clinical validity" is defined in the Public Consultation as demonstration of performance characteristics supporting the intended use of the IVD, including diagnostic sensitivity, diagnostic specificity, negative predicted value and positive predicted value. These two last elements are not currently mentioned in the IVD Directive. Some manufacturers who responded to the Public Consultation disagreed with this point and they, at least, would like to link the requirements of clinical validity to the newly proposed risk classification.

Clinical utility: "Clinical utility" of an IVD is defined as the demonstration of the potential usefulness and added value to patient management decision-making. Most of the respondents agreed not to endorse the introduction of the clinical utility concept in the new version of the directive, arguing that it would be difficult to include such a concept in a regulatory framework, particularly within the premarket assessment process.

Others

Conditional CE marking: Conditional CE marking could be useful in particular situations, such as in rare diseases or in pandemic situations, in which an easier, accelerated procedure for CE marking IVDs should be appropriate. Currently, Article 9(12) of the IVD Directive already addresses emergency situations on a national level, but the consultation respondents believed it advisable to have requirements applicable at the European level, since pandemic situations are rarely limited to a single Member State.

Companion Diagnostics: Companion IVDs are those devices developed and/or used in direct combination with specific medicinal products or which are co-developed with new medicinal products. Most of the respondents agree that these companion devices must be subject to the IVD Directive, but it is not clear into which class they will be introduced (probably Class C with involvement of a Notified Body) and how cooperation with the European Medicines Agency will be regulated.

Conclusion

At the moment, it is not possible to predict all the changes that will be introduced into the recast IVD Directive. These changes will likely include, but not be limited to, modifications related to the other medical devices directives and the results of the Public Consultation discussed here. With this in mind, it is possible that a new draft of the IVD Directive will be issued by the beginning of 2012; however, the process of final publication and adoption will take some time. Nonetheless, manufacturers marketing IVD devices in Europe, or planning to do so, should keep themselves informed of progress, because the IVD Directive recast could require very costly and time consuming changes in company operations if not considered in time.