



Revision of Europe's IVD Directive 98/79/EC

Lessons and results from the Public Consultation document.

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The European Directive 98/79/EC on in vitro diagnostic medical devices, or IVD Directive (IVDD), became operational in June 2000.¹ It provides Europe with one single regulation for in vitro diagnostics (IVD). Devices receiving the CE mark after one successful conformity assessment procedure can be introduced into the member states of the European Union and the European Free Trade Association, and two countries with which mutual recognition agreements have been established (Switzerland and Turkey)—32 European countries in all. More than 10 years of implementation also revealed weaknesses in the IVDD. For example, there is a consensus that its classification system is inadequate. Furthermore, scientific and technological evolutions, as well as new business trends in the IVD field—for example, the emergence of companies offering IVD testing as a service—created situations that are not effectively foreseen in the IVDD. A revision of the IVDD is needed to eliminate the weaknesses of the current version and to provide a regulatory framework within which issues arising from both technological progress and new business trends can be addressed.

The Public Consultation and Beyond

In June 2010, the European Commission published the Public Consultation document, inviting comments from stakeholders on 19 questions.² These questions were organized in the following sections and subsections:

1. Classification
2. Conformity assessment procedure
3. Scope
 - 3.1. Specific exemption for “in-house tests”
 - 3.2. Genetic tests
 - 3.3. Diagnostic services
 - 3.4. Point-of-care/near-patient in vitro diagnostic medical devices
4. Clinical evidence
 - 4.1. Clinical validity
 - 4.2. Clinical utility
5. Others
 - 5.1. “Conditional CE marking”
 - 5.2. Companion diagnostics

This list already indicates which areas are candidates for change or for inclusion in the IVDD. However, this does not mean that they will change or be included. And provided they do, it is still uncertain how they will change or appear in the directive.

The Public Consultation also focuses on technical issues and on subjects that are specific for IVD. However, in parallel, the recast of all European medical device directives is being prepared. Within that context, possible amendments of horizontal aspects, such as designation and monitoring of notified bodies, vigilance, market surveillance, and the need for further centralization are discussed. Any amendments resulting from that work will also be integrated into the IVDD. Therefore, the changes in the IVDD will not be limited to the subjects raised in the Public Consultation.

In February 2011, the results of the stakeholders' feedback were published.³ The European Commission received 183 responses: 69 from users (clinical laboratory associations, medical associations, hospitals and healthcare professionals), 44 from associations and laboratories



Based on this information, it looks rather unlikely that there will be major changes to the concepts of Common Technical Specifications, of batch verification by notified bodies, and of quality system certification for all but the lowest class of IVDs.

Self-testing devices currently have their own conformity assessment procedure, requiring a design-examination certificate issued by a notified body, but not a quality system certificate. If the GHTF model for classification and conformity assessment is followed, self-testing devices will no longer represent a class on their own and will become subject to conformity assessment procedures that include a quality system audit by a notified body. If so, this would have a significant impact on, for example, many small Own Brand Labelers of self-tests.

Scope: In-House Testing and Diagnostic Services

In the current IVDD, in-house testing (“home brew”) is excluded from the scope, if the “devices are 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.” This is often misinterpreted by companies offering diagnostic services, from within the EU or from outside. They often erroneously conclude that their in-house testing activities are also exempt from CE-marking. However, preamble 11 and article 9(13) of the IVDD clearly bring commercial IVD testing within the directive’s scope.

One may expect that the revised IVDD will clarify which in-house testing is exempt from the directive and which is not. The Public Consultation document suggests that the European regulators also are considering restricting the exemption to certain types of in-house testing, e.g., tests for rare diseases or tests in lower GHTF classes. The obligation for the testing laboratory to have an accredited quality system—in accordance with ISO15189, for example—or for the tests themselves to meet the directive’s essential and/or other requirements are other options that may be considered.

In addition to emphasizing or clarifying that diagnostic services are subject to the IVDD, specific requirements may be defined. These include requirements related to advertising and the provision of information to patients and users, especially when these companies directly advertise and communicate results to users.

It will be interesting to see how the revised IVDD will address the fact that increasing numbers of tests are offered, sometimes directly to the consumers, without the tests ever being physically placed on the market, and whether any such measures can be effectively enforced on companies that are not located within the EU but nevertheless offer their services to European consumers. The inclusion of offering a test for an EU citizen while he or she is within the EU into the definition of “placing a product on the market” is an option.

Scope: Genetic Tests

Genetic tests that have a medical purpose are already covered by the current version of the IVDD. However, the medical purpose of a genetic test is not always clear, such as with predictive tests and lifestyle tests.

The European Commission clearly intends to clarify the situation, and the Public Consultation primarily asked how this could be achieved. Moreover, there might be additional requirements or restrictions, especially for direct-to-consumer genetic tests. This idea was supported by 86% of the respondents.

Scope: Point-of-Care Tests

The current version of the IVDD has no specific requirement for point-of-care tests. One can argue that these are not necessary since manufacturers have to take the intended use of the device into account in design, risk management, labeling, etc. Nevertheless, more explicit requirements may improve the safety and effectiveness of these assays. Two-thirds of the respondents agreed with this and suggested, for example, that the manufacturers of these devices should demonstrate that the performance characteristics and the clinical validity are the same in the point-of-care setting as in a professional laboratory. The instructions for use



should also be suitable for lay-persons to carry out the test and to correctly interpret the results, including an explanation of the meaning of diagnostic sensitivity and specificity as well as of the meaning of positive and negative predictive values.

Whereas many of these suggestions seem to be justified, other suggestions are less realistic, such as the proposal to make the users of these tests subject to quality management system requirements. These might comprise external quality evaluation schemes and other measures intended to improve the reliability of the test results, but would be more difficult to implement in many point-of-care settings.

It is difficult to predict whether the revised IVDD will contain specific requirements for point-of-care testing or whether the current indirect approach will be maintained.

Clinical Evidence, Validity, and Utility

Within the current European regulatory context, there is little emphasis on clinical evidence. It is hardly mentioned in the IVDD. In practice, there is much more focus on analytical performance than on clinical evidence. European intended-use statements and performance characteristics are often expressed in analytical terms. Conformity assessment procedures, with or without a notified body, can be done with relatively little attention to the clinical validity of the test results. This is probably one of the major differences between the European and U.S. regulatory systems.

A large majority of respondents (88%) would like to see a clarification of the requirements for clinical evidence. A somewhat smaller majority (81%) would also like to see additional requirements for demonstrating clinical validity, including at least the demonstration of negative and positive predictive values. In contrast to competent authorities, notified bodies, and users, manufacturers are less supportive of this idea. The current approach, involving a relatively simple retrospective evaluation to establish the analytical performance characteristics of an IVD, will usually not allow establishing negative and positive predictive values since the tested sample populations do not usually reflect the expected prevalence of the tested disease or disease marker.

The idea of introducing requirements for clinical utility was only endorsed by one-third of the respondents. For the purpose of the public consultation document, clinical utility was defined as the demonstration of the potential usefulness and added value to patient management decision-making, but without considering health economics, reimbursement, or cost/benefit analysis. Stakeholders argued that the clinical utility should be assessed by the user in his specific context of use. In the case of novel markers, it cannot always be determined. Therefore, demonstrating clinical utility should not be part of a premarket assessment process.

The revised IVDD will likely clarify that an IVD assay must have the performance characteristics required to fulfill a clinical purpose. Moreover, requirements may be added on how to demonstrate clinical validity, possibly proportionately with the risk level of the test. The introduction of requirements to show clinical utility is less probable.

Conditional CE Marking

“Conditional CE marking,” i.e., the making available of IVDs without proper conformity assessment procedure for a limited period of time, might be useful in emergency cases (pandemics) or for creating timely access to tests for unmet medical needs. Such European-wide conditional CE marking could replace or complement the existing provisions for individual member states to allow tests without CE marks in emergency situations.

About three-quarters of the respondents thought that conditional CE marking would be useful, although there were questions about who would decide about such conditional CE marking and concerns that it might lead to the marketing of low-quality products. A majority of competent authorities prefer to keep the current system with the decision at the member-state level. Although it is recognized that the requirement for a full conformity assessment may be counterproductive in emergency cases and for tests for rare diseases, it is uncertain if and how the revised IVDD will contain new elements to address this.



Companion Diagnostics

Most IVDs that are used as companion diagnostics are not listed in Annex II of the current IVDD and are therefore self-certified by the manufacturer. The respondents to the public consultation almost unanimously underlined that companion diagnostics should remain subject to the IVDD and should also become subject to notified body review. Since companion diagnostics are in Class C of the GHTF model, the implementation of that model would bring them under notified body review.

For these products, some respondents expressed the requirement for demonstrating the clinical utility of the combination of the IVD and the medicinal product in the context of both the CE marking of the IVD and the marketing authorization of the medicinal product.

Manufacturers active in this field may also be interested in a recent paper on the codevelopment of pharmacogenomic biomarkers and assays in the context of drug development, published by the European Medicines Agency.⁶

In the revised IVDD, companion diagnostics will probably be put in a class that is subject to notified body review. It is unclear whether there will be specific requirements and whether there will be a common viewpoint between the regulators in charge of devices and those responsible for medicinal products.

Timing

Since the revised IVDD will not only include changes on the subjects treated in the Public Consultation, but also those from the recast of all the medical device directives, there is still a long way to go between now and the actual implementation of a revised IVDD. A draft is planned for the beginning of 2012. Then the text will have to go through a possibly lengthy approval cycle. After publication, the member states are given time to transpose the directive into their own legislation. The implementation date will then follow after that, probably not before the start of 2015.

Conclusion

Based on the Public Consultation document and its responses and also taking the possible changes from the general recast into consideration, it is safe to predict that the revised IVDD will have a significant impact on many IVD manufacturers. The European regulators' intention to increase safety will inevitably result in greater efforts and costs. Manufacturers should closely follow the subsequent steps in the legislative process and begin now to integrate the most likely changes into their regulatory strategies.

References

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