

The draft *in vitro* diagnostic regulation – revolution not evolution

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Abstract

With significant changes being discussed for *in vitro* diagnostic (IVD) legislation in Europe, this article looks at the proposals for more flexible, risk-based classification rules and available conformity routes, which will affect all IVD products.

Changes to the In Vitro Diagnostic (IVD) Directive 98/79/EC¹ and its sister directives, the Medical Device Directive 93/42/EEC² and Active Implantable Medical Device Directive 90/385/EEC,³ are currently being negotiated. However, unlike the other medical device directives, the planned changes to the IVD Directive are a quantum leap rather than an evolutionary step. The IVD Directive describes the regulation in Europe for tests used to provide information on human samples for medical purposes. The IVD Directive and medical device directives, while being sister directives, are currently and will remain separate because of the distinct nature of the devices, how they are used and the potential risk to individual patients and public health in general.

The IVD Directive, like the medical device directives, will become a regulation.⁴ The two regulations are being negotiated in parallel; the advantage of this is that, where possible, the structure and numbering of conformity routes will remain consistent, and so will the wording of common requirements. Regulations, unlike directives, come directly into force and there is no need for a transposition into national law; the current draft allows for a five-year transition period due to the magnitude of the changes facing the industry. Although there have been proposals that this should be limited to three years in line with the Medical Device Regulation,⁵ at present it is not expected to be first applied until 2015 at the earliest.

Since the IVD Directive was published in 1998 there have been considerable technological advances and the existing list-based classification has not been able to keep pace with these changes. The list-based classification appears simple but is rigid and cannot accommodate change. For example, although the first companion diagnostic pairing of Herceptin and HER2/neu was approved in 1998 (the year the Directive was published) the field of companion diagnostics was in its infancy and the BSE crisis was in progress during the final development of the IVD Directive. However, it was not until 2004 that transmission of new variant CJD through blood donations

was identified as a possible risk to the blood supply, and other diseases such as SARS Corona Virus were not identified until 2003. All of these events were after the publication of the Directive and therefore none of these devices are listed in Annex II of the IVD Directive and could not be reclassified without changes to the Directive itself.

As part of the revision to the IVD Directive, there was universal agreement that the classification needed to be changed and a flexible risk-based approach should be adopted. Canada and Australia already used forms of the Global Harmonisation Task Force (GHTF) classification⁷ and therefore this has been used as a model for the proposed IVD Regulation. The classification has four classes: A, B, C and D, where A is low risk and D is a high-risk device (see Table 1). The key difference between devices in Class D and C is that devices in Class D pose a high personal and also public health risk, for example, screening of blood donations; whereas Class C devices present a high personal risk but lower public health risk. Class C contains a variety of devices such as cancer markers, companion diagnostics and tests which may affect the foetus. Class A devices are the very low risk devices such as specimen receptacles and many instruments, and Class B contains anything not listed on D, C or A.

The proposed classification rules described in Annex VII are similar to but not identical to those described in the GHTF document or the Canadian or Australian regulations. Each of the rules is applied in turn, as shown in Figure 1; if more than one rule is appropriate then the higher classification applies, for example a self-test device for HIV is in Class D. The new classification will be more flexible and logical; however, as this is a significant departure from the existing classification, it will result in many borderline issues. The IVD Technical Group of the Medical Device Expert Group (MDEG) has therefore created a subgroup to develop a guidance document based on the draft rules to enable manufactures to classify their devices as soon as possible and therefore determine the potential impact to the regulatory requirements.

Figure 2 summaries the conformity routes available. The IVD Regulation will retain the Common Technical Specification (CTS)⁶ and batch verification for Class D devices; in addition the notified bodies will be required to inform the European Commission so that a new group, the Medical Device Coordination Group (MDCG), can decide whether it also wishes to review the submission. The notified body is required to take into consideration its comments. The MDCG will provide technical support to the Commission and in addition to these reviews will contribute to the assessment of notified bodies and the development of guidance. A network of reference laboratories will also be established to independently test to the CTS, provide input to the preparation of the CTS and can perform batch verification for Class D devices.

In common with the draft medical device regulation, the bar is continuing to rise. One of the key areas where expectations are likely to increase is the clinical requirements. The draft regulation says clinical performance studies shall be performed unless it is duly justified to

Figure 1: Proposed application of the classification rules in Annex VII of the draft IVD Regulation.

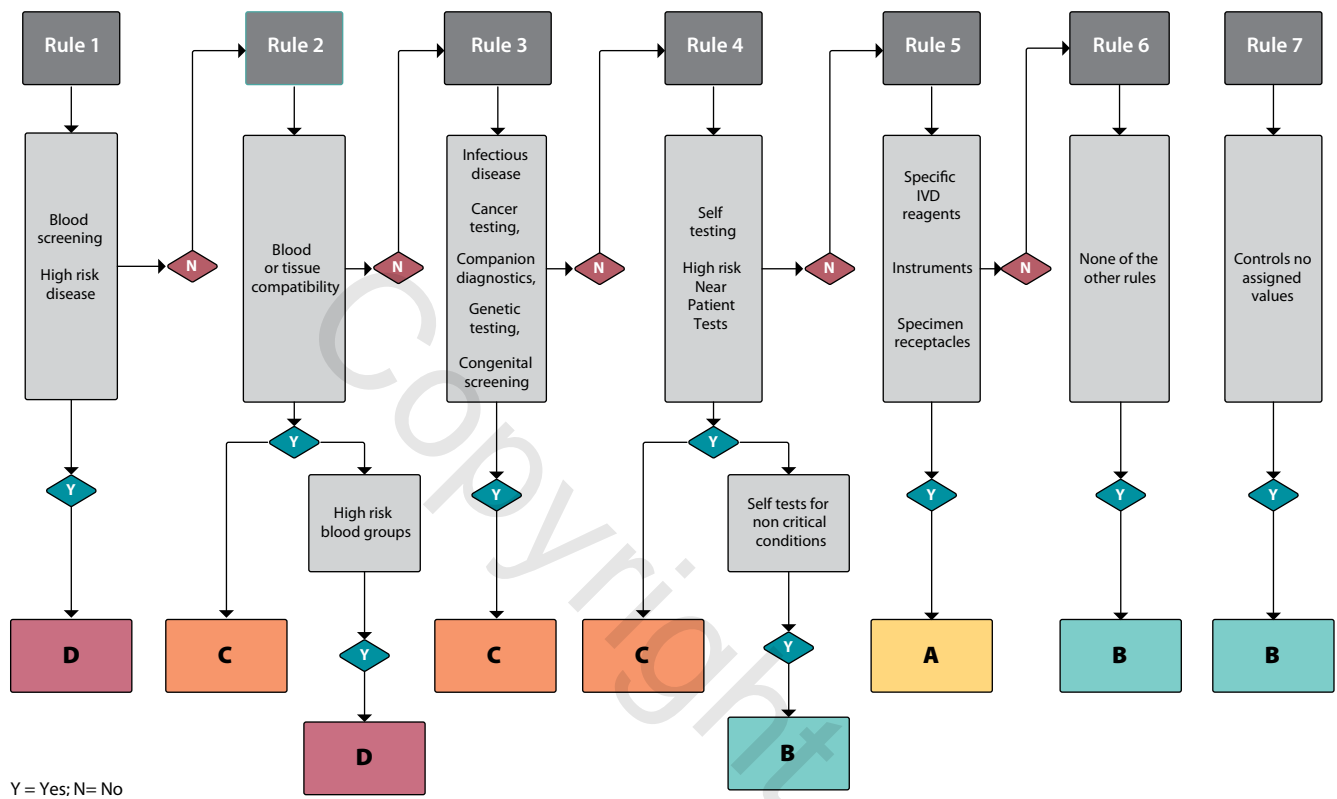


Figure 2: Proposed conformity routes of the draft IVD Regulation.

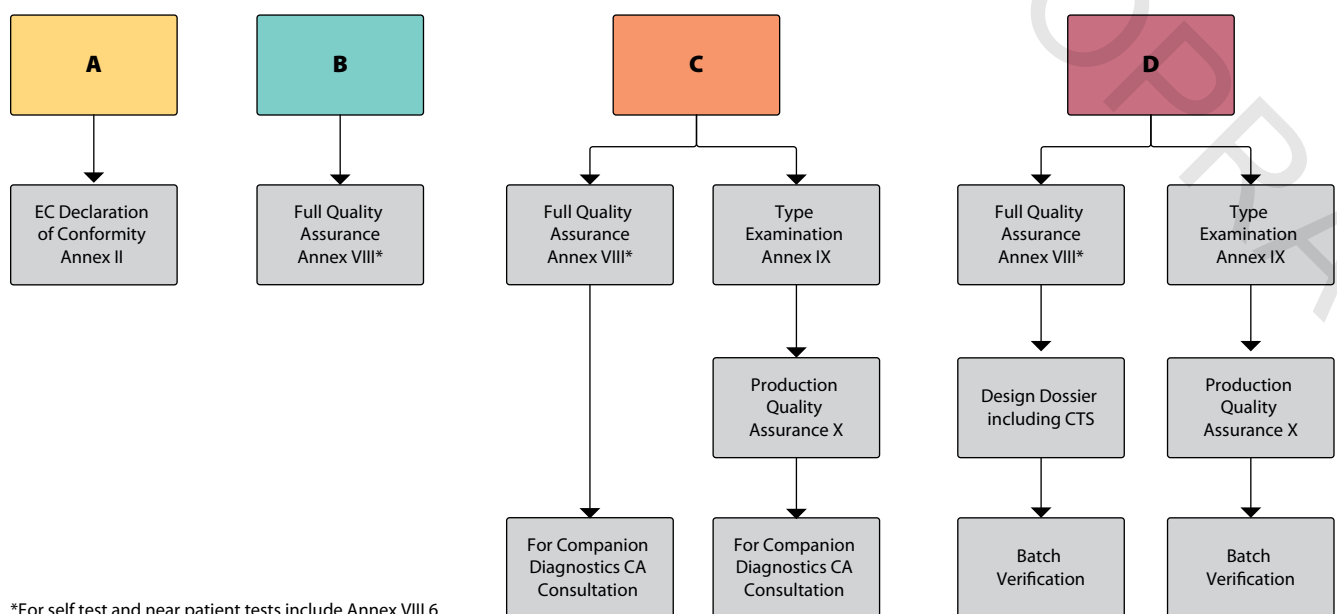


Table 1: Proposed classification of the draft IVD Regulation based on the GHTF principles.

Class	Risk level	Device examples
A	Low individual risk and low public health risk	Clinical chemistry analyser, specimen receptacle
B	Moderate individual risk and/or low public health risk	Vitamin B12, pregnancy self testing, urine test strips
C	High individual risk and/or moderate public health risk	Blood glucose self testing, Rubella, human genetic tests, companion diagnostics
D	High individual risk and high public health risk.	HIV blood donor screening, HIV blood diagnostic.

rely on other sources of clinical performance data. Also they state that, where post-market follow-up is not deemed necessary, this shall be duly justified and documented in the post-market surveillance plan. A clinical performance study establishes the ability of a device to yield results that are correlated with a particular clinical condition or a physiological state in accordance with the target population and intended user. The study will be performed in circumstances similar to the normal conditions of use of the device. This suggests that we will see an increased number of performance evaluations and post-market studies rather than data solely derived from within company verification studies.

Some of the last documents released by the GHTF provide guidance on clinical studies for in vitro diagnostic devices and are a valuable source of information, now located on the International Medical Device Regulatory Forum (IMDRF) website as part of the GHTF archive. These documents include:

- Clinical Performance Studies for In Vitro Diagnostic Medical Devices⁸
- Clinical Evidence for IVD Medical Devices – Key Definitions and Concepts⁹
- Clinical Evidence for IVD Medical Devices – Scientific Validity Determination and Performance Evaluation.¹⁰

Many of the other significant changes which are introduced in the draft IVD Regulation are in common with the draft medical device regulation; for example, there are significantly increased requirements for economic operators, authorised representatives and those who re-label and repack devices, including registration requirements. Manufacturers and authorised representatives will be required to have a qualified person with two to five years regulatory experience in the IVD field, depending on education. The IVD industry is much smaller than the medical device or pharmaceutical industries and therefore many IVD companies use experts from the medical device industry to fill quality and regulatory positions; these requirements may be a challenge for industry to meet.

In conclusion, the forthcoming changes to IVD legislation will have the same or greater impact as the initial introduction of the IVD Directives. All products will be affected and the technical documentation for all products will need to be updated to meet the new essential requirements and clinical data expectations. The way that companies do business may also change as distributors and importers will have to be capable of meeting regulatory requirements as well as the manufacturer. Considering the magnitude of the changes, manufacturers need to ensure they understand these changes and the impact to their business. They should also talk to their notified body to understand the plans and level of resourcing, to make sure it meets the needs of the company. In many cases, manufacturers will be using a notified body for the first time and will

need to build a new relationship. Although 2015 may seem very distant, past experience suggests that, with the magnitude of work required, time will pass quickly and manufacturers will require the full transition period to make all devices compliant with the new regulation.

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