NEW IVD REGULATIONS

The key to getting the transition right

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Alterations to the legal framework for in vitro diagnostic (IVD) devices are aimed at improving the current situation across Europe, but getting the timing right for the implementation of changes is essential to ensuring that the new regulations result in a better system for IVDs rather than a bureaucratic quagmire.

The long and resource-intense process of revising a law at the European level always mobilises European institutions and requires extensive discussions and consultations with stakeholders. Since the goal is a new law that will improve legal frameworks in a significant way, legal texts are revised where necessary to accomplish specific goals.

Against that backdrop, the framework regulation for *in vitro* diagnostic (IVD) devices is currently under revision. The European Parliament and Council are discussing a proposal that will shape the regulatory landscape for IVDs in Europe for the coming decade and beyond.

The original IVD directive (IVDD - 98/79/EC) is being revised at the procedural level, as there are innovations that need to be implemented even in the regulatory area. Many of these regulatory innovations stem from an international dialogue that took place under the Global Harmonisation Task Force (GHTF), which is now continuing in the International Medical Device Regulators Forum (IMDRF). Changes have to be made to address the technical and scientific shortcomings of a law that was developed and discussed nearly two decades ago (although only published in 1998, discussions on the current IVD Directive began in earnest in 1994-95).

A lot has changed in two decades, and the new legislation is aimed at addressing those changes. Much more emphasis is now being placed on the growing fields of genetic testing and companion diagnostics, although regulators are respecting the idea that overall concept and legislation remain technology independent. Experience garnered from the IVDD will also result in changes to the way IVDs will reach labs and – ultimately – patients.

An overview of major changes

From a scientific perspective, the biggest change in the works for IVDs is the necessity for manufacturers to provide clinical evidence for an *in vitro* diagnostic test prior to its being CE-marked and made available for diagnostic use. This clinical evidence needs to include not only the test's analytical performance (already required today) but also a demonstration of an assay's scientific validity. The latter is generally accomplished by establishing a link between the analyte being measured and one or more clinical conditions. Another prerequisite will be to provide clinical evidence for the use of the test.

This in essence shifts responsibilities from lab clinicians to manufacturers when it comes to establishing a lot of this information and determining when a test is intended to be used, although of course ultimately the laboratory will decide how to use and report results. These requirements could potentially result in manufacturers having to go back and further test existing assays in order to ensure that clinical evidence has been demonstrated.

A key change to the regulation will be the stricter control of assays developed in-house (known in the US as 'laboratory-developed tests'). It has always been the case that by developing an assay in-house, a laboratory acted as a manufacturer of an IVD device, but for the most part this took place under an established exemption. It is essential that laboratories continue to develop assays, as they are not only the main source of innovation for the sector but also in many cases the only source of tests for certain rare conditions. However, regulators are keen to see some level of control over this practice,

both in the interests of public safety and to ensure that the exemption for in-house assays is not used as a means to circumvent the intent of regulations.

When it comes to classification and conformity assessment, although all IVD devices are subject to the same requirements, in a nutshell they must all be safe and fit for their stated purpose. At the control level, a distinction must be made based on the risk they pose so as to properly allocate authorities' limited resources. Those IVDs that would pose a high risk to patients or public health if they were to fail are for good reason the focus of control by authorities.

Changes in risk classification

The current IVD directive lists the *in-vitro* diagnostic devices considered to be of high risk or the highest risk. Although this system has the advantage of clarity (a device is either on the list or not, there is very little leeway for interpretation) it has proven difficult to keep these lists up to date. A system that does not rely on constant development of lists has therefore been proposed. In it, the lists will be replaced with a set of rules. Essentially, if an IVD plays a role in maintaining public health (for instance, ensuring the safety of the blood supply) it is considered of the highest risk class. Classification will be based on the impact diagnostics have on patients, with assays for the diagnosis and management of life-threatening diseases considered to be higher risk than routine biochemical analysis. The new set of conformity assessments stemming from the classification will result in much stricter manufacturer oversight by third party notified bodies, which will be inspecting a much wider range of facilities and reviewing the designs of more IVDs than ever before. Following the revision, it's expected that up to 90% of all IVDs will be subject to some level of review by notified bodies.

Transitioning into these and other key changes encompassed in the new regulation will take time and resources. Authorities, the industry and labs will not be able to adapt to the new rules governing the IVD world overnight. The key question is – how much time will it take exactly? On the one hand, all of these changes will provide benefits in

the regulation of *in-vitro* diagnostic devices, and as such it would be beneficial to expedite their implementation. On the other, an implementation that is carried out too quickly could lead to unnecessary increases in the cost of IVDs, and could also potentially result in some level of disruption in device supply.

Since the medical devices framework is being revised at the same time as the IVD regulation, it is tempting to compare or even regard the two processes as one and the same. However, while both medical devices and IVD regulations are undergoing an update to the regulatory processes, the changes to IVD regulations will be much more profound as they are adjusted to reflect scientific and technological progress.

Setting up a timetable

It is interesting to see the approach that the European Parliament has taken to the transition. While selecting different elements of the legislation that need to be implemented quickly to ensure relevant, safety measures are rapidly adopted, it also allows for a longer transition for those measures that are more resource-intensive and require more time to implement for laboratories, authorities and manufacturers. Specifically, this is the timing that the EP is proposing:

- Within six months, notified bodies will be subject to stricter control measures and will have to demonstrate competence in the specific fields in which they will be operational. It is quite possible that not all notified bodies will be maintained following these requirements.
- Within 12 months: National authorities across Europe will need to establish and begin employing better mechanisms for cooperation to ensure the system is truly pan-European, and to safeguard European citizens across the union. In addition the authorities should have by this point agreed rules of implementation necessary for the practical adoption of other aspects of the legislation.
- Within 18 months, manufacturers will need to have implemented the new system for unique device identification. This will enable IVDs to be traced throughout the supply chain all the way to the laboratories where they are ultimately used. Because of the new rules, laboratories may need to adapt on how they track their use of supplies. This aspect represents both an opportunity and a challenge.
- Within 24 months the new rules for vigilance would kick in. Coupled with unique device identification, this will allow for much better monitoring and reporting of incidents across Europe to better identify trends and potential health concerns.
- The remaining provisions would be fully implemented within 60 months. These provisions include changes to the way in which in-house assays are regulated, the adoption of the new conformity assessment and classification rules, and the establishment of clinical evidence for all existing devices.

In practice, this will mean that the majority of IVDs will need to be modified at some level before compliance with the new regulation is possible – even if that only means including additional information regarding the clinical evidence of the device and updating the labels to reflect the involvement of notified bodies in the assessment of the devices.

Other jurisdictions seeking to implement this kind of regulation for IVDs (such as Australia's Therapeutics Goods Administration) have shown that a five-year transition period is necessary to ensure that all stakeholders are able to comply fully with new requirements. The staggered approach proposed by the European Parliament will ensure that key safety provisions are rapidly implemented, while also allowing sufficient time for the more complex implementation of the rest of the legislation.