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INDUSTRY'S VIEW ON THE FUTURE OF *IN VITRO* DIAGNOSTIC (IVD) LEGISLATION IN EUROPE

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INDUSTRY'S VIEW ON THE FUTURE OF *IN VITRO* DIAGNOSTIC (IVD) LEGISLATION IN EUROPE

For the last 15 years, the European regulatory landscape for *in vitro* diagnostics (IVDs) has been shaped by Directive 98/79/EC. During this time, patients and laboratories within Europe have been able to access novel technologies with relative ease, while the overall safety record of IVDs in the European Union (EU) has remained excellent. There have been a handful of safeguard clause actions since the implementation of the IVD Directive (where authorities intervene to restrict an IVD from the market). Given that there are over 40,000 types of IVDs on the market in the EU, these cases show that only a tiny fraction of IVDs have resulted in real safety concerns.

However, although the overall record of IVDs has been positive under Directive 98/79/EC, the system has also revealed some significant shortcomings that need to be addressed.

Shortcomings of Directive 98/79/EC

Some of the issues for IVDs are also shared with other medical devices, in particular the question of the supervision and competence of Notified Bodies. For some time there has been concern about the fact that Notified Bodies provide different levels of oversight for manufacturers, and that some Notified Bodies fail to embrace their role in ensuring that IVDs are both safe and effective. Although within the IVD sector there are only 26 EU Notified Bodies (compared to 77 for medical devices), divergences between Notified Bodies have still been a matter of concern.

Divergences in the interpretation of the legal requirements have also turned out to be one of the weaker points of Directive 98/79/EC. It was implicit that Member State authorities would need to collaborate with each other and the Commission in order to address fully many of the implementation questions that arose over time. However, the only mechanism envisioned for formal collaboration within the IVD Directive was the Article 7 Committee, which turned out to be ineffective in addressing all of the issues that arose because of procedural issues and also because of a great uncertainty as to who should initiate action at an EU level. Although this was partially addressed through the development of a set of guidance documents published by the European Commission (the MEDDEV guidance documents), these documents were in no way binding to Member States and discrepancies were not always resolved satisfactorily through this process. Divergent interpretations led to a proliferation of national registries, and different national decisions on how certain IVDs fit within the regulatory framework. For instance, the case of how IVD software is regulated has been very strongly debated over the last few years and remains a subject of divergent interpretation amongst Member States.

While the questions around Notified Bodies and divergence of interpretation are shared with other medical devices, a very specific shortcoming has also become readily apparent. The classification system for IVDs under the Directive is based on two lists of IVDs contained in Annex II (Lists A and B). However, this list-based approach has been shown to be inadequate in reflecting technological advances and the introduction of novel devices into the IVD field – this was poignantly highlighted by IVDs intended to screen the blood supply for variant Creutzfeldt-Jacob disease. Although the Annex II lists were eventually updated to reflect the nature

of such assays, the process – which took approximately four years – was far from satisfactory.

Attaining international regulatory convergence

The European Commission has been involved in the development of a set of principles for regulatory convergence at an international level, mainly through the activities of the former Global Harmonization Task Force and, more recently, through the International Medical Device Regulators Forum (IMDRF). A case has been made for the implementation of these principles at an EU level as not only do they represent the state-of-the-art in regulatory processes but also because such convergence in regulatory requirements would help in the dissemination of medical technologies around the globe. This would result in predictable benefits to the users of IVDs and boost the competitiveness of the EU sector in this field.

As a consequence, the European Commission initiated a consultation in 2010 for the revision of the IVD Directive, the outcome of which is now under consideration by the European Parliament and the Council of the European Union. The Commission has proposed to change the IVD legislation into a Regulation, which means that the official EU text will be directly applicable throughout all Member States, thereby removing any issues relating to the transposition of the Directive. The discussions in Parliament with regards to the IVD legislation are happening in parallel with those of the medical devices legislation, which was presented simultaneously to Parliament and with which there are a number of common elements.

Medical device regulation should not prevail

Unfortunately, the carefully laid plans for the revision of the legislative frameworks for both medical devices and IVDs took a backseat in December 2011 when Poly Implant Prothèse (PIP) breast implants made headlines around the world. The French regulatory authority made a formal recommendation for the explantation of PIP breast implants following allegedly fraudulent activities within PIP that resulted in the use of industrial grade silicone to fill the implants as a cheaper substitute for medical grade silicone which was specified in the design of the breast implants.

The PIP case highlighted a number of failings within the regulation of medical devices, and by extension IVDs, which the European Commission decided to address as a matter of urgency. This eventually coalesced into a set of 'immediate measures' to be adopted under the existing legislation to address the immediate shortcomings. These immediate measures will affect the way Notified Bodies are run, and will also lay the foundations for the establishment of a European system for Unique Device Identification (UDI) to help facilitate the traceability of devices.

Under the immediate measures, Notified Bodies will see two major changes. Firstly, the control by the Competent Authorities will be significantly more stringent, with the establishment of accreditation criteria and a peer review system put in place for multiple authorities to verify jointly the activities and competences of Notified Bodies. Secondly, Notified Bodies will have an obligation to carry out unannounced inspections (these were already allowed under the current system, but for a number of reasons were virtually never used). This will mean that Notified Bodies may show up at production sites and take samples of IVDs for further testing to ensure that the performance of the IVDs is in line with the requirements of the Directive.

Implementing a UDI system

The European Commission has been laying the groundwork for the implementation of a system which will allow for the identification of devices throughout the supply chain until the moment of use. This system involves two aspects:

- a physical representation of a unique code on the IVD, generally in the form of a barcode (although other technologies, such as radio frequency identification, might be used);
- establishment of a database to connect the device identification to additional information concerning the device.

The full UDI system will only be implemented in the EU with the new Regulations; however, the immediate measures from the Commission aim to ensure harmonisation among all the Member States for the development and implementation of the UDI system.

Once the immediate measures come into force, industry will need to prepare for the proposed Regulation from the Commission having legal force and taking effect. Estimating the time when this will happen is difficult as it depends on the negotiations between the European Parliament and the Council, but the earliest possible date for publication would be mid-2014 (assuming a first reading agreement). This timing will also depend on whether the Council will be ready in time. Given that the parliamentary elections will take place in the summer of 2014, there is no clear indication if an agreement will be made.

Adopting a new classification system

The proposed Regulation contains a number of points that will have a very significant impact on the way IVDs reach the market in the EU. The adoption of new classification rules, abandoning the old lists, is at the heart of many of these changes.

According to the proposal, IVDs will be classified into four risk classes (A to D). Class D IVDs are those whose failure would present a public health risk – mainly IVDs used in ensuring the safety of the blood supply (both those that establish the blood type and those used to detect the presence of pathogens) and those IVDs which are used for the primary detection and confirmation of high risk diseases with a high risk of propagation (e.g. human immunodeficiency virus, hepatitis). Classes A through C represent devices that present a varying degree of risk to individual patients, with Class C being IVDs that present the highest individual risk and Class A devices those with the lowest risk.

Due to the nature of the classification rules, many IVDs will see their risk classification increase when compared to the situation today. The consequence of this is that, in general, IVDs will be subject to a much greater degree of control than before. All Class B, C and D IVD manufacturers will need to have a Quality Management System that is certified by a Notified Body. Additionally, for Class C devices, design dossier reviews will be mandatory for a representative sample of the IVDs, and all Class D devices will need a full design dossier review.

Companion diagnostics

Certain IVDs will be subject to additional requirements as companion diagnostics, which are defined in the legislation as 'devices specifically intended to select patients with a previously diagnosed condition or predisposition as eligible for a targeted therapy'. Companion diagnostics will all be subject to design dossier review but, in addition, mechanisms are being put in place to ensure co-ordination between the European Medicines Agency (who is responsible for the approval of the medicinal product which relies on the companion diagnostic) and Notified Bodies (who are responsible for the design review of the companion diagnostic themselves). The details of this co-ordination are one of the main points of discussion on the table.

Near patient testing systems

Specific conformity assessment procedures have also been identified for near patient testing systems, in particular design dossier review. There are also certain specificities with regards to the

classification of near patient testing systems involved in blood glucose and blood gas determination (these are both Class C devices). Other near patient testing systems are classified according to the risks presented by the analytes they are measuring.

Regulating software as an IVD

The question of regulating software as an IVD is fully addressed in the proposal and there is no doubt that software which meets the definition of an IVD will fall under the new IVD Regulation and will be subject to specific requirements with regards to design and lifecycle management. This reflects, to a large extent, the work that has been carried out in MEDDEV 2.1/6 on medical software.

Getting the Regulations right

A number of changes are happening that are shared by the IVD and medical device proposals. Specifically, the means of controlling Notified Bodies (which echoes a lot of the work from the immediate measures), the establishment of a UDI system, and the reinforcement of the vigilance system, are all important aspects in which the two Regulations are co-ordinated.

In addition, both Regulations seek to regulate not only manufacturers and Authorised Representatives but also the distribution chain of devices, and in order to do so new requirements are included for importers and distributors. At this time the requirements of the different economic operators are overlapping somewhat but a consensus is emerging that the manufacturer and his Authorised Representative will be responsible for the device itself, while distributors and importers will be responsible for the distribution chain under their control.

Unfortunately, there also seems to have been some confusion in the introduction of certain aspects of the medical device legislation into the IVD proposal. For instance, single-use devices have been highlighted as a concern, which stems from the problems of reprocessing medical devices. However, this has never been a concern for IVDs as once a reagent has been used up it is nearly always impossible to re-use it, while instrumentation is never single use. Another similar situation has arisen with the inclusion of provisions for devices with a measuring function – all IVD instrumentation by its very nature gathers information and therefore has a measuring function, in fact the entire Regulation is in place to ensure a proper control of the information that comes from that measurement. Therefore, adding the generic requirements from the medical devices Regulation to the IVD field creates an additional layer of paperwork, but does not increase the safety or performance of the devices in any significant way.

Control mechanisms for IVDs have been maintained and reinforced. The Common Technical Specifications, which have been so successful in setting requirements for the highest risk IVDs, remain in place and are likely to be expanded, probably to be used in other areas such as companion diagnostics. Reference laboratories are also given a formal role within the proposal: they will serve as a source of scientific advice for the Commission and Member States and play a role in the actual testing of IVD samples (e.g. those collected by Notified Bodies during their unannounced visits). This will clearly help prevent situations where the quality and/or performance characteristics of an IVD vary outside the acceptable specifications.

Systematic clinical evidence

The final key change in the legislation is the need for IVD manufacturers to provide clinical evidence on their devices prior to the devices reaching the market. Clinical evidence is composed of three sets of information all of which need to be established for all IVDs:

- Analytical performance is the first component

of clinical evidence. Here there is no real variation from what is required today: the various analytical performance characteristics of an IVD such as trueness, precision, analytical sensitivity and analytical specificity all need to be determined.

- Clinical performance is the second component of clinical evidence and deals with the way in which a device actually performs within a clinical setting. It can be established through the actual use of the IVD in the setting where it is intended to be used. For existing IVDs, this information should be available or could be gathered through collaboration with users. However, novel devices might require clinical performance studies, unlike the performance evaluation that happens today.
- Scientific validity of the analyte being measured is the third component that needs to be established. In essence the clinical value of the measurement needs to be demonstrated before the IVD goes on the market. For well-established assays (e.g. blood glucose, cholesterol, potassium), the scientific validity can be demonstrated by referencing the existing scientific literature on the subject, but very novel IVDs, especially if they are looking at new analytes, will need to assess the scientific validity. This is expected to have a major impact in the area of genetic testing and oncology, where novel markers are routinely being explored for the purposes of diagnosis.

Furthermore, clinical evidence is not something that is simply established when the IVD comes to the market. Manufacturers will have an obligation to establish a system of post-market follow-up for the device to ensure that changes to the IVD or new scientific information are assessed to see if they have an impact on the clinical evidence pertaining to the IVD.

A five-year transition period

As a result of all the changes that IVDs will need to go through, especially the reclassification and the need to establish clinical evidence, the IVD proposal includes a five-year transition period. Certain parts of the system will transition faster, such as the establishment of a UDI system and the increased control of Notified Bodies, but for the most part manufacturers will have five years to bring their IVDs into compliance.

Compliance, however, is not going to be trivial and the impact is going to be significant. The European Diagnostic Manufacturers Association has estimated that the costs associated with the reclassification alone will be approximately 200 million Euros for the entire sector. Many of the new requirements will necessitate the gathering of information early on in order to be compliant by the time the Regulation is fully applicable. This means that once the final Regulation has been published, all IVD companies should start to prepare for compliance.

Early preparation is the key

Although it will be at least 2019 before the implementation of the IVD Regulation is complete, it will represent a major change in the way IVDs reach the EU market. In part, the changes will align EU legislation with that of other regulators. For instance, Canada and Australia are also adopting the same classification, which will potentially ease the regulatory complexity, but at the same time the transition will inevitably bring a period of regulatory uncertainty. By preparing early for the coming changes, IVD companies will be in a better position to manage this uncertainty and ensure an uninterrupted supply of diagnostic tools to physicians and patients alike.

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