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EU Agrees on New Medical Device and IVD Regulation

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Representing one of the largest medical device markets in the world, the European Union (EU) recently underwent a significant regulatory shift. On June 15, the EU Council, Parliament, and Commission agreed on final regulatory texts that will govern medical devices and *in vitro* diagnostic medical devices (IVD), reportedly beginning late 2019. The agreement seeks to fill the regulatory gaps uncovered as technology evolved faster than the current regulatory regime, last updated in 2007.

The regulations will strengthen the rules for placing medical devices on the market, as well as tighten market surveillance and vigilance. The regulations establish requirements for quality management systems, clinical evaluations, and gathering clinical data, with specific duties for all economic operators, including manufacturers and distributors.

Economic Operators

While medical device and IVD manufacturers have many of the same duties as before, the new regulations are more prescriptive. Under Article 8, for example, manufacturers must:

- Record and report incidents and field safety corrective actions, and document and maintain a risk management system;
- Conduct a clinical evaluation according to the regulatory requirements in Article 49 and Annex XIII;

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- Draw up and regularly update their devices' technical documentation according to the requirements in Annexes II and IIa (specific requirements for the contents of the technical documentation);
- Comply with the EU unique device identifier (UDI) requirements; and
- Ensure procedures are in place that allow the manufacturers and their devices to maintain conformity to the regulation.

Authorized representatives similarly play a role in the current regulatory framework. Significantly, the new regulations hold authorized representatives and manufacturers jointly and severally liable for defective devices.[1] In addition, the regulations add new economic actors, such as Importers and Distributors, and assign regulatory duties to them as well. Importers and Distributors are specifically defined and are responsible for, among other items, verifying that the product has a corresponding Declaration of Conformity and that the manufacturer is identified.[2]

The Medical Devices and IVD Regulations also require the manufacturer to designate a person who is responsible for regulatory compliance. Such individuals must have the requisite experience in the field of medical devices, shown through a combination of education and experience in medical device regulatory affairs.[3] In general, this new position should be an internal position for the manufacturer, except that micro and small enterprises may employ a contractor who is permanently and continuously at their disposal.[4] The person responsible for regulatory compliance is responsible for ensuring:

- The conformity of the devices is checked against the quality management system before the device is released;
- The technical documentation and the declaration of conformity are drawn up and kept up to date;
- The manufacturer complies with the post-market surveillance operations, including its vigilance reporting obligations; and
- If the device is investigational, a statement that the device conforms to the general safety and performance requirements according to Annex XIV section 4.1.[5]

Device Classification

Medical devices will continue to be classified into four risk-based classes: I, IIa, IIb, and III. While the rules that govern classification may seem familiar, some medical devices are up-classified, changing their regulatory profile dramatically. For example, some spinal implants, currently in Class IIb, will be Class III according to Rule 8 of Annex VII. In addition, there are new classification rules for new technologies such as nanomaterial (Rule 19), and software (Rule 10a).

Classifying an IVD will be fundamentally different from the current regulatory framework. The new IVD Regulation introduces four risk-based classes of IVDs that are based on the Global Harmonization Task Force's classification scheme:

- Class A products are low-risk products, products for general laboratory use, and specimen receptacles;
- Class B products include self-tests for the detection of pregnancy, for fertility testing, determining cholesterol levels, and for the detection of glucose, erythrocytes, leucocytes, and bacteria in urine;
- Class C products include tests for infectious agents such as sexually transmitted agents, or for detecting such agents in cerebrospinal fluid or blood. Class C products also include companion diagnostics; and
- Class D products are products that test for high-risk conditions such as HIV, hepatitis, and ABO blood grouping and tissue typing for transfusion.[6]

To help IVD manufacturers transition to the new classification scheme (and resulting conformity system), the IVD Regulation includes a five-year transition period.

Clinical Data

The regulations highlight the crucial role of clinical data throughout the lifecycle of the medical device or IVD. To this end, an entire chapter is devoted to the clinical evaluations that manufacturers are required to perform. The clinical evaluation is a "systemic and planned process to continuously generate, collect, [analyze,] and assess the clinical data pertaining to a device in order to verify the safety and performance, including clinical benefits, of the device when used as intended by the manufacturer."[7] Specifically defining the clinical evaluation as a continuous process that is built into the manufacturer's quality management system signals the intent that the clinical evaluation should be performed throughout the device's life cycle. While clinical evaluations have always been a part of the device's technical documentation, the Medical Devices Regulation states that manufacturers "shall plan, conduct and document a clinical evaluation in accordance with [Article 49] and Part A of Annex XIII."[8]

One way to accumulate clinical data is through a clinical investigation. The Medical Device Regulation creates a requirement to conduct clinical investigations for both Class

III devices and implantable devices, even if the implantable is not a Class III device. However, if the device is equivalent to one the manufacturer put on the market and the device's clinical evaluation "is sufficient to demonstrate conformity of the modified device with the relevant safety and performance requirements," then an additional clinical investigation is not required.[9] In these cases, notified bodies are instructed to ensure the manufacturer's post-market clinical follow-up plan is "appropriate and includes post market studies to demonstrate the safety and performance of the device."[10] Also, if a new device is equivalent to another that was placed on the market by another manufacturer, the two manufacturers have an agreement in place that allows the second manufacturer "full access to the technical documentation on an ongoing basis," and if the original device's clinical evaluation was performed according to the new regulatory requirements, then a clinical investigation is likewise not required.[11]

The regulations also include specific requirements for starting and running a clinical investigation. For example, Article 50 states that a clinical investigation shall be carried out for the purpose of establishing and verifying:

- That the device is designed, manufactured, and packaged in a way that it conforms to the definition of a "medical device;"
- The clinical benefits of a device are what its manufacturer specifies; and
- The clinical safety of the device and to determine any side-effects and if these side effects constitute acceptable risks when weighed against the benefits of the device.[12]

Article 50 also includes conditions that must be met before a clinical trial may begin, and Article 50aa includes informed consent principles that must be followed.

Quality Management System Requirements

Manufacturers will continue to have the same requirement to operate a comprehensive quality management system. However, the Medical Device and IVD Regulations specify what that system must include and how the manufacturer must operate it. These additional requirements seem to emphasize the system's continuous loop of feedback, analysis, and action. Annex VIII, the conformity assessment that includes a review of the quality management system and technical documentation, instructs notified bodies to pay particular attention to the procedures and techniques the manufacturer uses to address:

- The strategy for regulatory compliance, including how the manufacturer identifies the legal requirements, qualification, classification, and choice of conformity assessment procedures;
- Identifying applicable general safety and performance and how the manufacturer meets these requirements; and
- The risk management system.[13]

One sub-system of the quality management system that explicitly requires the feedback loop is the post-market surveillance system. According to Article 60a, the post-market surveillance system "shall be suitable to actively and systematically gather, record and [analyze] relevant data on the quality, performance and safety of a device throughout its entire lifetime, to draw the necessary conclusions and to determine, implement and monitor any preventive and corrective actions."[14] Data that the post-market surveillance system gathers is used to:

- Update the risk-benefit ratio for the risk management, design, manufacturing information and the labeling;
- Update the clinical evaluation;
- Update the summary of safety and clinical performance;
- Identify needs for preventive, corrective, or field safety corrective actions;
- Identify possibilities to improve the usability, performance, and safety of the devices;
- Contribute to post-market surveillance for relevant other devices; and
- Detect and report trends.[15]

In this way, manufacturers should be able to use the data gathered through the post-market surveillance system as inputs in the various sub-systems as a way to continuously improve their products.

Notified Body Audits

Manufacturers will directly feel the regulatory changes through notified body audits. There have been reports that, in preparing for the regulatory changes, notified bodies are already requesting more, and more robust, clinical data and clinical evaluations and are performing longer audits to incorporate the additional requirements. Even though the regulations are not yet formally published or enforced, many Competent Authorities have reportedly instructed notified bodies to gather more evidence for some devices and have questioned notified bodies' rationales for allowing certain devices on the market. Additionally, the contentious unannounced audits will be a permanent and explicit requirement of the manufacturer's conformity assessment.[16]

Next Steps

Following the regulations' entry into force, or official publication, the medical device regulations will have a three-year implementation period (five years for some provisions for IVDs) before the regulations are fully applicable and enforced. However, there will be interim enforcement periods for some requirements. Medical device and IVD manufacturers should carefully read the final regulations when they are published to adequately build a plan to comply with the new regulations.

1. Harmonized Proposal for a Regulation of the European Parliament and of the Council on medical devices, Article 9.4a. (*Hereinafter* Medical Devices Regulation).
2. Medical Device Regulation Article 11.2
3. *Id.* at Article 13.1.
4. *Id.* at Article 13.1a.
5. *Id.* at Article 13.2.
6. Harmonized Proposal for a Regulation of the European Parliament and of the Council on *in vitro* diagnostic medical devices, Annex VII.
7. *Id.* at Article 2(32).
8. *Id.* at Article 49.1.
9. *Id.* at 49.2a.
10. *Id.* at 49.2a.
11. *Id.* at 49.2aa.
12. Medical Devices Regulation, Article 50.1.
13. *Id.* at Annex VIII.3.2.
14. *Id.* at Article 60a.3.
15. Medical Devices Regulation, Article 60a.4.
16. *Id.* at Annex VIII.4.4.