

DEVELOPING OPHTHALMIC DEVICES IN A CHANGING EU REGULATORY ENVIRONMENT

Companies introducing new medical devices in Europe must understand the broad-ranging revisions of regulations now being implemented.

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Companies developing medical devices such as IOLs must comply with relevant regulatory processes to gain certification for the sale of their goods in the European community. These same companies must now ready them-

selves to deal with changes in the medical device regulations for the EU market.

The European Parliament and EU member states have undertaken a broad-ranging revision of the EU Medical Devices Directives (MDD) through new pending legislation. In the future, companies wishing to develop, market, and sell medical devices will need to understand and comply with these proposed revisions to EU law.

Companies must carefully consider their strategies for responding to the regulatory changes, which present new risks but also new opportunities. Those that ignore the coming changes will be poorly prepared to react to the updates in regulatory requirements and may lose out to competitors that more quickly comply with the new environment.

REGULATION FAIL

Any company that wishes to sell medical devices within the European Union is aware of the need to gain the CE Mark from regulatory authorities within the member states to demonstrate that the product conforms to the prevailing MDD. Companies are also aware of the need to adhere to the MDD and to approach a notified body toward the end of the design and development phase of a product. However, they may not be aware of the changing regulatory environment in the aftermath of recent scandals that damaged the reputation of the regulatory community. (For more on the Poly Implant Prothèse scandal, see *What You Need to Know: New EU Medical Device Regulations*, on page 43,



AT A GLANCE

- The European Parliament and EU member states have undertaken a revision of MDDs through pending legislation.
- In its proposal for regulation, the EU gave notified bodies authority to conduct unannounced audits, making it clear that better conformity with regulatory requirements is to be expected from manufacturers.
- Since the MDDs were proposed in September 2012, the Commission and EU Parliament have been engaged in the diplomatic processes of obtaining agreement from the member states and shaping the new legislation.

and the article's coinciding *EU Regulatory Glossary* for definitions of regulatory terms.)

Failure by the regulatory authorities to detect irregularities in breast implants¹ and faulty hip implants² raised important questions: Was the relationship between industry and notified bodies sufficiently independent? How effective was the flow of product-safety information to the notified body, and how quick was the reaction of the notified body to this information?

These scandals rocked public confidence in the medical device industry and its regulators. The high-profile failures highlighted the shortcomings of existing medical device regulations, and there has subsequently been a call to action to reestablish confidence in the effectiveness of the system of regulatory approval and the recertification process for products already on the market. The public suspects that industry emphasizes profit over patient safety and that current regulatory processes are not sufficient to minimize risks to patients.

HOLES IN THE REGULATORY PROCESS

In the aftermath of the PIP scandal in 2010, it took until February 2012 for the European Union to officially respond to the member states with a call for immediate action to tighten controls and increase surveillance in an attempt to restore public confidence in the medical device regulatory process, especially for high-risk products.³

In a proposal for regulation in September 2012, several problems were identified, including the fact that certification was easier in some member states than others. A need was recognized to harmonize the application of the MDD uniformly across the member states and to improve the standards of certification of notified bodies by the member states' competent authorities. The proposal stated that the European Union should have tighter control over the notified bodies, and these organizations should be provided with auditors with expertise relevant to the device type. By giving the notified bodies the power to conduct unannounced audits, the EU proposal made it clear that better conformity with regulatory requirements is to be expected from manufacturers.

The proposal also recognized that the EU regulatory process lacks adequate postmarketing surveillance, and now the requirements are to be enhanced. For example, manufacturers must continue to monitor and report adverse events; such reports are to be centralized in Eudamed, a European medical device database accessible to all notified bodies to improve information exchange.⁴ The proposal also introduced a device identification system to enable long-term traceability of products in the market once they are certified, including details about specific production batches. These unique identifiers would facilitate the monitoring of safety and performance of the devices throughout the product lifecycle.

UNANNOUNCED AUDITS AND OTHER FIXES

The suggested changes in the MDD will have a profound effect on developers and manufacturers of medical devices. One significant change is the recommendation that notified bodies must carry out unannounced audits at least once every third year, and more often for higher-risk devices (see *Unannounced Audits* on page 45 for more information).⁵ Industrial developers and their manufacturers must therefore look ahead in crafting contractual agreements in order to ensure that access will always be available to the notified body to inspect production processes and that competent staff will be available to assist the auditors on such unannounced audits (see *General Advice for the Organization of Unannounced Audits*).

Audits should take more than 1 day and be completed by at least two auditors, according to the recommendations. The auditors must have the opportunity to test recently produced samples and to check documentation.

The sampling criteria and testing procedures must be defined before the audit takes place according to the risk profile of the product. The auditor must be compensated for the audit, including the costs of any device acquisition required to carry out the audit or testing and security arrangements.

These requirements will be onerous for a manufacturer who may be producing small batches of products, the production of which might not coincide with the timing of the audit. The requirements will also be onerous for the notified bodies, especially the need for additional trained auditors who have expertise in the relevant product field.

Additionally, manufacturers will need to employ more qualified individuals who are responsible for regulatory compliance. These people must ensure that the conformity of devices is appropriately assessed before a batch is released, technical documentation and declarations of conformity are kept up to date, and reporting obligations are fulfilled. Such individuals are expected to have either a university degree in a relevant discipline and at least 2 years of professional experience in regulatory affairs or in quality management related to medical devices, or 3 years of professional experience in regulatory affairs or quality management systems. It is expected that this will add up to 30% to the regulatory costs of medical devices in the future.

There are also two new requirements for clinical evaluation of devices, the first of which is carried out as part of the certification process and the second of which is carried out at regular intervals once the product has been placed on the market. These evaluations must follow a defined and methodologically sound procedure, including either a critical evaluation of relevant scientific literature, where the relevance of the literature is judged as containing equivalent information related to the safety, performance, design,

30%

The predicted rise in the regulatory costs of medical devices due to manufacturers' need to increase their efforts to be compliant with regulations in the future.

GENERAL ADVICE FOR THE ORGANIZATION OF UNANNOUNCED AUDITS

(Taken directly from the European Commission website¹)

In order to ensure that notified bodies are in a position to perform unannounced audits, some modalities, such as the following ones, should be considered:

1. Unannounced audits in premises of the manufacturer or its critical subcontractors or crucial suppliers should be foreseen in the contractual arrangements between the notified bodies and the manufacturers. If a visa is needed to visit the country where the manufacturer is located, the contractual arrangements should contain, as an annex, an invitation to visit the manufacturer at any time and an invitation that leaves the date of signature and the date of visit open (to be filled-in by the notified body). The contractual arrangements should also contain, as an annex, similar invitations issued by the critical subcontractors or crucial suppliers.

2. The contractual arrangements should foresee that the manufacturers continuously inform the notified bodies on the periods when devices falling under the notified bodies' certificates will not be manufactured. The contractual arrangements should authorize the notified bodies to end the contract as soon as their permanent unannounced access to the premises of the manufacturer or its critical subcontractors or crucial suppliers is no longer assured.

3. The contractual arrangements should furthermore cover the measures to be taken by notified bodies to ensure the security of their auditors. The contractual arrangements should provide for a financial compensation for the unannounced audits including, where applicable, the device acquisition, its testing, and security arrangements.

1. Recommendations. European Commission website, <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2013:253:0027:0035:EN:PDF>. Accessed January 19, 2015.

and intended purpose of the device (with emphasis that the literature must demonstrate compliance with relevant general safety and performance requirements) or a critical evaluation of all reported clinical investigations that provide data for evaluation, not just selected reports that support an evaluation.

Any demonstration of conformity on the basis of non-clinical testing has to be duly substantiated in the technical documentation. Postmarket clinical follow-up will also become a continuous process that requires constant updates on the clinical evaluation as a normal part of the product lifecycle, especially with regard to the reporting of adverse effects.

STATUS OF LEGISLATION

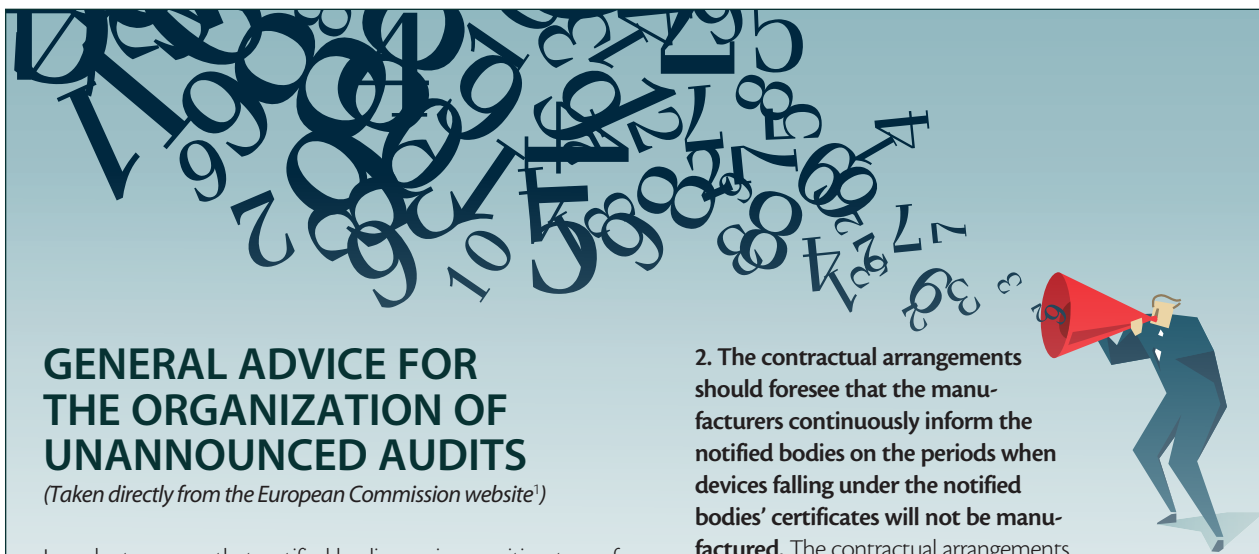
The European Commission produced a proposal for new regulations to amend the MDD in September 2012.⁶ Since then, the Commission and EU Parliament have been engaged in the diplomatic processes of obtaining agreement from the member states and shaping the new legislation.

The Italian EU presidency of 2014 failed to reach the politi-

cal agreement required before informal so-called *trialogue* negotiations can commence among the representatives of the European Parliament, Council, and Commission. When a compromise agreement has been reached, a health rapporteur will take the agreements through the formal acceptance processes of voting in the Environment and Public Health Committee, followed by voting in the full Parliament, and then final approval by the EU Health Ministers to achieve new legislation.

The Latvian and Luxembourg EU presidencies in 2015 will need to build on the work started by the Italians to find a consensus. The latest progress report from the Italian Presidency indicates that a number of unresolved issues must be addressed.⁷ It is not expected, however, that the 2015 presidencies will give these activities a high priority, so it is likely that the legislation will not progress before the Dutch Presidency in 2016, when it is hoped that agreement can finally be reached.

Nevertheless, the new EU medical device guidance documents⁸ should be understood as supporting and clarifying existing directives. This means that manufacturers, notified bodies, and competent authorities are already working within them.



PREPARATIONS WITHIN IROC

IROC Science specializes in providing consulting services for translational projects in ophthalmology by supporting the industry with applied research, product development, and clinical trial services. IROC has prepared itself to react to the changes described in this article with two specific measures:

- 1 We have devised tools and services to support our customers in undertaking postmarket surveillance clinical studies.
- 2 We are keeping abreast of developments in the regulatory environment for medical devices so that we can give our partners informed advice on regulatory issues and prepare them for audits.

CONCLUSION

The frequency of unannounced audits of device manufacturers in the European Union is already increasing, according to a June 2014 update by European Commission staff. As of April 2014, more than 40 notified bodies had finalized or were finalizing revised procedures, and most were launching trials or had carried out audits of device manufacturers, the report stated.⁹ ■

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