EU Medical Device Regulatory Framework: Practical Impact of New Regulations

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Regulatory

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Dr. Boutrand has been involved in more than 60 public presentations or publications on topics related to the preclinical or clinical evaluation of medical devices. He is also registered as an expert on biological safety of medical devices for a national health agency.

The EU has the second largest medical device market globally, with emerging technologies typically available 2-3 years ahead of the US market and 5 years ahead of the Japanese market. Medical device manufacturers have been attracted to the EU device market because of faster approvals, regulatory directives that are less strict and more innovation-friendly than in the US, and overall shorter time-to-market for medical devices. Thus there has been a progressive increase in the number of global manufacturers submitting applications for medical device approvals (ie, a CE ["conformité Européenne"] Mark) in the EU, as well as an increase in the number of patients in the EU seeking to use medical devices. Device makers are choosing to have their products not only registered in the EU first, but often only in the EU.

However, two recent high-profile medical device cases have created controversy within the EU medical device regulatory framework and led to a push to replace the former, less restrictive EU Medical Devices Directive (MDD) with more formalized (although still not binding) device regulations and biocompatibility testing requirements. This white paper reviews the context that led to the political momentum for more regulation of medical devices in the EU, the potential impact of the new medical device regulations, and the effects this change may have on the time frame for approval and implementation of medical devices.

The Controversies

Poly Implant Prothèse (PIP) Breast Implants

Potential health concerns with silicone breast implants manufactured by PIP were being discussed in the medical literature as early as 2006-2007 (Lahiri 2006; Adams 2007; Berry 2007). In 2009 surgeons in France began reporting an abnormally high rupture rate with PIP's breast implants, and in 2010 the French medical safety agency (AFSSAPS) issued a recall of PIP implants. By March of 2010 PIP was in liquidation, and facilities inspection had revealed that the company was substituting unapproved industrial-grade silicone in their implants in place of approved medical-grade silicone (Keogh 2012), a substitution that could potentially cause increased health hazards in the event of rupture. A 2012 UK report on PIP implants, however, found that although PIP implants were more likely to rupture (about double other brands), the PIP silicone was not toxic or carcinogenic (Lancet 2012 MHRA; Keogh 2012). The French government recommended the removal of PIP implants and announced that the 30,000 French women who received PIP implants were entitled to have them removed at no cost (Horton 2012; O'Dowd 2011). In December 2011 a fraud lawsuit was filed against PIP by CNAM, France's state health insurance fund, for the use of unapproved silicone.

Due to the fallout from the early stages of the PIP scandal, the European Parliament issued, on June 11, 2010, a non-binding call to the EC to create solutions to prevent recurrence of events such as those leading to the recall of PIP implants in France.

In January 2012, US Center for Devices and Radiological Health (CDRH) Director Jeffery Shuren remarked on a conference call that the EMA's device approval standards were in effect treating European patients like "guinea pigs," causing an immediate furor (Richwine 2011). A January 17 editorial in the Lancet about the PIP scandal (Lancet 2012 FDA) came down on the side of the US FDA's more stringent device approval process, and an internal FDA report in April 2012—"Unsafe and Ineffective Devices Approved in the EU That Were Not Approved in the US"—listed 12 classes of substandard or high-risk medical devices approved for sale in Europe but not the US. The report was later made public in May 2012 (US FDA 2012).

Metal-on-Metal (MOM) Hip Implants

Stemmed MOM hip implants were originally designed as an alternative in younger osteoarthritis patients, for whom long-term total hip replacement device survival is poor (Smith 2012). However, MOM prostheses with a larger head (ball) size (≥36 mm) in particular have shown higher failure rates than other head surfaces such as ceramic-on-ceramic or metal-on-polyethylene (Smith 2012). In this case the US was at the forefront of device use (35% of US hip replacements in 2009 were MOM implants), with more than 500,000 MOM prostheses patients in the US at elevated risk of device failure, according to a commentary published alongside the Smith paper (Sedrakyan 2012). There are also concerns about the release into the body of metals such cobalt and chromium with large-diameter MOM heads (Prentice 2013). The problem caught the attention of the EU, where an estimated 100,000 patients have undergone MOM hip replacement, and a committee was formed to explore the safety of MOM implants, with a particular focus on hip prostheses (SCENIHR 2012). The controversy rose to scandal status recently when it was revealed that 650 French patients were fitted with hip prostheses with modifications that had not been approved in the EU (Samuel 2013).

The New Device Regulations

As the executive body of the EU responsible for proposing and implementing legislation, the European Commission (EC) first put the MDD into place in June 1993 (Council Directive 93/42/EEC) in an attempt to harmonize medical device regulation across the EU member states. Before the PIP breast implant scandal, the last time the MDD had been amended was in 2007, and the directives were scheduled to be updated again in 2012 (The 2007 amendments to the MDD became fully enforceable on March 21, 2010. The main areas affected included conformity assessment, changes

applicable to medical plastics, classification criteria [Class I-III], transparency within the EU, and clinical evaluation requirements).

The transition to the full regulations is expected to be completed in or near 2018.

Due to the fallout from the early stages of the PIP scandal, the European Parliament issued, on June 11, 2010, a non-binding call to the EC to create solutions to prevent recurrence of events such as those leading to the recall of PIP implants in France. In response the EC called for open public consultation on a recast of the MDD. The open period ended in 2010 and proposed legislation from the EC was submitted on September 26, 2012. The European Parliament voted to release the new legislation quickly (by 2014), with specific provisions coming into force during the period from 2015-2018.

2014 Regulations: Significant Changes

At the conceptual level, the new legislation will require 1) stricter device approval rules for Notified Bodies (regulatory arms of member states); 2) stricter preclinical and clinical evaluation of new medical devices; 3) centralized review of data for high-risk devices (including review of risk class proposed by manufacturer); and 4) unannounced inspections for high-risk devices. These changes will strengthen EU medical device regulations, increase their scope, enhance the powers of Notified Bodies within their member state but allow for greater regulation of Notified Bodies across EU states, and put in place mechanisms to facilitate coordinated reactions from member states in case an issue arises.

The transition to the full regulations is expected to be completed in or near 2018. The most significant changes will 1) extend the scope of medical device directives to include some products without a medical need (eg, cosmetic devices such as breast implants or non-corrective contact lenses) as well as devices utilizing non-viable human tissue or cells (eg, human collagen pre-filled syringes); 2) require strict selection of a Notified Body based on prespecified criteria developed with the individual EU member state; 3) require a "second look" by Notified Bodies at data for high-risk devices to increase compliance; and 4) require unannounced inspections to decrease biocompatibility gaps and increase conformity for approval of high-risk devices (**Table 1**).

2014 Regulations: Conclusions & Action Items

No study has categorically shown that more patients have been injured in the EU than in the US due to different regulatory frameworks and standards. On the other hand, US patients certainly have been affected by the lack of availability, or delay in availability, of some medical devices due to the stricter US regulatory system, and there have been cases of US patients traveling to the EU to get implants not yet approved in the US.

Table 1. Practical Consequences of Changes to Medical Device Directives

	CHANGE	POTENTIAL IMPACT
Scope of Devices Regulated	• Extension of scope to include some cosmetic devices • Extension of scope to include devices using non-viable human tissues or cells	• Increased work for Regulatory Affairs (RA) • Increased demand/shortcut for RA staff • Increased consultancy and training needs
Validation of Notified Bodies	• Notified Body (NB) selection based on stricter and more detailed criteria enforced across the individual EU member states • Monitoring of NBs made subject to joint assessments by other EU member states • Rotation of the NB personnel at appropriate intervals required	• Stricter requirements from surviving NBs • Potential shortage of resources from validated NBs • Increased demand for NBs • More questions/answers from NBs • Increased demand for biocompatibility assessments • Potential for increased costs, delays, and longer timelines for manufacturers
Device Testing & Inspection	• NBs to provide list of reference laboratories validated for testing • Summary of safety and performance of high-risk devices, including key elements of the supporting clinical data, must be made publicly available • Summary will be reviewed by NBs • "Second look" by NBs required for high-risk devices to ensure biocompatibility/compliance • NBs authorized to conduct or require additional or confirmatory testing • NBs required to review the data from reference laboratories to decrease information gaps • Unannounced factory inspections of high-risk devices by NBs (eg, once per year for Class III devices)	• More emphasis on test laboratory selection • Increase in release testing • Less tolerance of noncompliance to current standards (eg, number of extracts, methods, and reports based on current version of standards) • More need in biocompatibility/ performance test training • Increased communication (both ways) on biocompatibility and performance with end users/ atients • More strict interpretation of standards regarding information gaps • Potential for increased costs, delays, and longer timelines for manufacturers • Less tolerance of biocompatibility gaps • Increased scrutiny on change controls: new provider, impact of minor changes, monitoring plans of conformity, etc
Surveillance	• Increased postmarketing surveillance • Enhanced coordination of vigilance cases analysis (trend analysis) and reactions	• Potential for increased costs/litigation for manufacturers
Manufacturer Staffing	• Within the manufacturer's organization a qualified person will be responsible for regulatory compliance	• Increased costs • Increased resources needed, particularly as qualified personnel become more in demand

The new EU regulations aim to keep rapid access to the market, remain cost effective, and continue to be supportive of innovation while providing enhanced protection of public health. Healthcare professionals, for example, will be provided with better information on the benefits for patients, residual risks, and the overall risk/benefit ratio of treatments (European Commission 2012). The goals are to evaluate more data (clinical and non-clinical), to coordinate communication among member states, and improve harmonization of Notified Bodies for more competent and timely reviews of biocompatibility data. To some extent, manufacturers will benefit from clearer rules, ease of trading among member states, and a level playing field that benefits innovative small and medium-sized manufacturers (European Commission 2012).

It is in the best interests of device manufacturers to prepare for the regulatory changes as soon as possible. To prepare for the phasing in of these regulations it is recommended to:

1. Secure regulatory authority resources (see Further Reading, below)
2. Increase training to ensure full compliance in Biocompatibility Assessments
3. Update submission files before expected 2017 due date of the application
4. Prepare for higher costs of the overall assessment and submission fees

Further Reading

- MDD revisions and new regulations documents can be found at http://ec.europa.eu/health/medical-devices/documents/revision/ and http://ec.europa.eu/health/medical-devices/documents/guidelines
- CE Mark guide: http://www.lne-america.com/quality-news-faqs/free-guide-ce-marking.html

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Ted Gorski, NAMSA Founder

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