

The Impact of Regulatory Compliance on European Medical Device Manufacturers Selling into the US Market

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Abstract

The European medical device trade organisation estimates the global market for medical devices at E184 billion. The global market has two main players, with the US representing 43% and the European Union claiming 30%. To standardise compliance and regulatory measures of this expanding global medical device market, there is an extensive cooperation of agencies including the FDA, ISO, EC and the International Committee on Harmonisation. These agencies are continuously revising mandatory regulations to dictate requirements needed to approve medical device pre-market approval, quality systems, clinical study evaluations, sales & marketing promotion, adverse event reporting and conformity with business practices to ensure compliance at all levels in any given organisation.

These regulations apply to companies designing medical device product specification and development (especially those in the Class III category), European companies manufacturing (cGMP) in the US and initial importing of medical device products into the US. In addition to pre-market requirements, the Harmonisation of agencies requires commitment to assuring consistent compliance. Medical device companies seeking market growth in the US or in the European Union will need to stay abreast of specific compliance standards to remain competitive and in accordance with regulatory requirements.

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Background

Although there are varying estimates about value, Eucomed, the European medical device trade organisations, estimates the global market for medical devices at E184 billion, with the United States and Europe representing the two largest sectors. The US holds 43% of the global market while Europe claims 30%. Just five European countries – Germany, France, Italy, the UK and Spain - account for approximately 78% of the E55.2 billion European market.

The US, European Union, and EU member states are distinguished in the global medical device market, not only in size but also in production capacity. The US is the world's largest producer of medical devices. Moreover, the US medical device sector is dominated by large companies, operating globally, while 80% of the European medical device industry is represented by companies with fewer than 250 employees. Logically, European companies have focused considerable attention on the export of their products, both inside and outside the EU, as a means of expanding market share.

The continued strength of the US market will be fueled by the same demographics that propel the global medical device market forward. According to an article by Dr. Rosanna Tarricone, Eucomed Economic Affairs Director, the 65+ population will grow from 71 million in 2000 to more than 130 million in 2050. During that same period, the 80+ segment will increase from 15 million to 53 million during the same time period. Overall, the percentage of people 65 and older will grow from 3.2% in 2000 to 12% of the global population in 2050. Most important, what distinguishes the US in the near future from other global markets is the money appropriated for health care and the receptivity of residents to new medical technologies.

A Harmonised Global Approach

Harmonisation of global standards for the development, production and sale of medical devices is a frequently expressed goal of national, regional and international organisations. To that end, there has been extensive cooperation and effort by agencies including the US Food and Drug Administration (FDA), the International Standards Organisation (ISO), the European Commission (EC) and the International Committee on Harmonisation.

Notwithstanding the efforts of these organisations, there remain a sometimes confusing array of overlapping regulations and regulating organisations. The European Commission's three "New Approach" directives, also known as the Medical Device Directives, harmonised rules affecting the movement of medical devices throughout the European Union.

ISO 13485:2003 is the prevailing quality system standard for medical devices and the basis for the CE mark that confirms a company's compliance with essential requirements of the Medical Device Directives' quality standards and allows the sale of the manufacturer's medical devices in the European Union. The ISO does not require a specific quality system such as 13485, but companies will be well served – both in obtaining the CE mark and in complying with FDA's QSR requirements, by implementing the harmonised standards of 13485.

Although 13485 is very similar to FDA's QSR, there are notable differences. For example, there are clear distinctions in the area of adverse event reporting. The ISO requires "customer focus" as part of management's responsibility to identify customer-related feedback about the quality of medical devices and related services. Under the ISO standards, customer feedback can be obtained from multiple sources including user surveys and peer-reviewed journals. The FDA's adverse event reporting requirements, conversely, specifically focus on issues of product safety. Healthcare providers, patients and responsible parties must be provided with a formal program to lodge complaints about products, and companies are required to document that complaints, report to FDA about complaints, and take appropriate corrective and preventive measures to assure product safety.

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In 2005, the EC published a proposal to amend the 1993 Medical Directive 93/42/EEC. Key amendments have been proposed in these areas:

- Clinical data requirements would become more specific and ethics committees would be required to review clinical investigation plans rather than only consent forms. Perhaps most significant, clinical evaluation would apply to all devices, not just those in the higher risk Class II and Class III categories.
- Classification for devices would be amended and clarified.
- Notified bodies would evaluate design documentation for samples of product lines carrying CE Marks when they conduct quality systems audits.

- Creation of a database with information on products, manufacturers, authorised representatives and conformity assessment certificates, allowing regulators to share information with each other and with the public.
- Classification of borderline and combination products would be clarified. Products will be classified depending on the product's primary mode of action rather than its intended purpose. The regulatory requirements associated with the classification also would be clarified for medical devices that incorporate drugs.
- Software will qualify as an active medical device, with a corresponding validation requirement.
- Electronic labeling is not specifically allowed under the amendments, but the Commission is permitted to adopt measures allowing instructions to be provided by means other than paper format, opening the door to e-labeling.

It is worth noting that the rapid evolution of medical device technology inevitably will require new regulations. As nanotechnology, increased use of software and electronics, and the rapidly evolving application of human tissue become more prevalent, tighter regulations can be anticipated to ensure patient safety and reduce risk of adverse events.

US Regulatory Requirements

The FDA is one of the oldest and, arguably, most restrictive, national regulatory bodies. Medical devices that are approved for sale in the US can be sold anywhere in the world, but the reverse is not true. The FDA states:

"Foreign manufacturers must meet applicable United States medical device regulations in order to import devices into the US even if the product is authorised for marketing in another country. ...FDA does not recognise regulatory approvals from other countries."

For medical device companies, regulatory approval to import products into the US requires registration of establishment, listing of devices, and Pre-market Notification 510(k) or Pre-market Approval.

- Initial importers of medical devices must register their establishment with FDA. An initial importer is defined as any importer who furthers the marketing of a device from a foreign manufacturer to the person who makes the final delivery or sale of the device to the ultimate consumer or user, but does not repackage, or otherwise change the container, wrapper, or labeling of the device or device package. Initial importers are also subject to Medical Device Reporting (MDR) under

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CFR 803; Reports of Corrections and Removals under 21 CFR 806; and Medical Device Tracking under 21 CFR 821, if applicable.

- The medical device must be classified before the manufacturer can determine what type of pre-marketing submission/application is required for FDA clearance to market in the US. FDA has established classifications for approximately 1,700 different generic types of devices, grouping them into 16 medical specialties, or panels. Each type of device is assigned to one of three regulatory classes based on the level of control necessary to "...assure the safety and effectiveness of the device." The classes range from Class 1, which carries the least regulatory restriction, to Class III, which is regulated most stringently.
- Class I and II: The typical requirement is a 510k. Class I and II devices that are exempt are subject to specific limitations.
- Class III devices require a premarket approval application, unless the device was on the market prior to the passage of the medical device amendments in 1976 or substantially equivalent to such a device.

Beyond Approval: Compliance

While great attention is paid to the approval process, it is only the first step in an ongoing compliance relationship with the FDA. Notes the FDA:

"Foreign firms that manufacture medical devices and/or products that emit radiation that are imported into the United States must comply with applicable US regulations before, during, and after importing into the US or its territories."

Beyond actions required for device approval, manufacturers must comply with long-term requirements including manufacturing in accordance with the FDA's quality system regulation and medical device reporting of adverse events. In particular, foreign manufacturers should note FDA's admonition that, "As with domestic manufacturers, foreign manufacturing sites are subject to FDA inspection."

FDA's compliance requirements are similar to those of the EC, but they are not identical. Unlike most European standards, FDA's regulations are not voluntary. They typically require extensive documentation, not only in the expected phase of clinical study, but also in the distribution of information and the training of employees. A brief look at the compliance requirements post-approval and the enforcement perspective of FDA highlights the potential complexity of compliance throughout the manufacturing, marketing/sale, and post-marketing phases.

QSR, cGMPs and SOPs

The acronyms of compliance are burned into the regulations themselves. FDA's Quality System Regulations (QSR) are pervasive, setting a quality standard that finds common ground with ISO 13485:2003. Under QSR, manufacturers are required to assure compliance with Current Good Manufacturing Practices (cGMPs). As is evident from the "current" in the cGMP title, regulations establishing which practices are compliant change regularly, with each change requiring adjustments that can range from minor to major. Finally, the cornerstone of cGMP compliance is the Standard Operating Procedure (SOP), which articulates the specific process and procedure required to perform any individual task. SOPs must be written, distributed and validated in prescribed formats.

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Marketing/Sales

All labels, package inserts, service manuals, instructions for use, advertising materials or promotional materials used in connection with the marketing and sale of medical devices are regulated by the FDA. Labeling requirements are regulated under several regulations including Good Manufacturing Practices (21 CFR 820), while advertising and marketing may come under the scrutiny of FDA, the Federal Trade Commission, US Department of Justice (DOJ) or the US Department of Health and Human Services (HHS).

In recent years, FDA has substantially increased its monitoring of the Internet, with a corresponding increase in the number of Warning Letters it has sent companies. While some of those Warning Letters, particularly concerning Class I devices, have focused on false claims made by manufacturers, other Warning Letters have addressed inconsistencies between statements on websites and approvals given by FDA for the product's sale in the US.

The role of HHS and DOJ in specific areas of medical device marketing deserve special attention, since they fall outside the immediate control of FDA and may be less apparent to non-US manufacturers. In FY 2006, the US government obtained settlements and judgments in excess of \$3 billion through prosecution of cases under the Anti-Kickback Statute and False Claims Act. Under both laws, the issue was the financial relationship between medical product manufacturer and healthcare providers. Both the Anti-Kickback Statute and False Claims Act make provisions for criminal and civil penalties – and both can be brought by whistleblowers, who have played the lead role in the government's growing prosecution efforts.

Adverse Events

Certainly, safety concerns are not reserved for the US. They are, however, highly visible. The recent recall of hundreds of thousands of implantable pacemakers, stents and cardioverter defibrillators has alerted millions of patients, doctors, regulators and medical device companies to the potential outfall of failed safety procedures, including adverse event reporting.

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Enforcement Priorities

FDA's enforcement activities extend from clinical trials through post-marketing and cover violations as diverse as inadequate training of personnel to a failure to maintain adequate procedures for corrective and preventive action. Notwithstanding the range of potential violations, several common denominators become evident through a review of FDA Warning Letters. Those common denominators are inadequate procedures, documentation and knowledge. A look at recent FDA warning letters highlights the role of these common denominators.

- On April 24, 2006, FDA issued a Warning Letter to a European company that manufactures battery operated and computerised wheelchairs. Among the violations identified through FDA's inspections were violations of cGMP requirements under the QS regulation. FDA noted, "Your firm's management with executive responsibility failed to ensure that an adequate and effective quality system has been fully implemented and maintained at all levels of the organisation, as required by 21 CFR 820.20." FDA cited specific examples, including a failure to ensure adequate staffing to handle customer complaints, a failure to ensure adequate employee training to handle customer complaints, and a failure to distribute approved and current quality system procedures to the affected employees at their designated working areas.
- In May 2006, a Warning Letter was sent to a firm located in the UK, citing noncompliance with cGMP requirements. Significant violations included a failure to adequately investigate the cause of nonconformities relating to product, processes and the quality system; a failure to identify the actions needed to correct and prevent recurrence of nonconforming product and other quality problems; a failure to adequately establish and maintain procedures for implementing corrective and preventive action

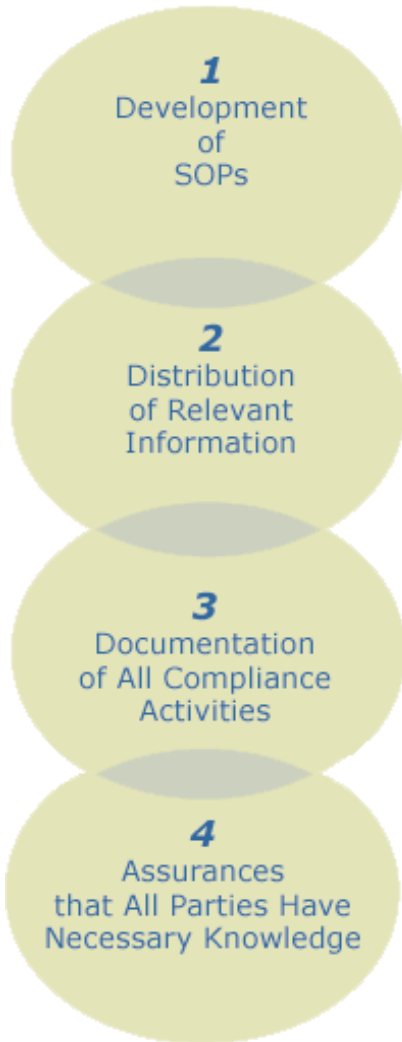
- In March 2006, FDA issued a Warning Letter after determining that a US-based company acted as a “specification developer and an importer” of a medical device. According to FDA, “Entities performing the functions of specification development or an initial distributor (importer) of medical devices are classified as medical device manufacturers within the meaning of 21 CFR 820.3(o) and, therefore, are subject to the quality System regulation.” Specific violations identified during FDA’s inspection included a failure to maintain and provide all GMP records for FDA’s inspection; a failure to evaluate and select potential suppliers, contractors and consultants on the basis of their ability to meet specified requirements including quality requirements, and to document the evaluation; and failure to establish and maintain procedures related to responsibilities including documentation of servicing, control and distribution of finished medical devices, design of the device, and evaluating complaints.
- In late 2005, FDA issued a Warning Letter to a manufacturer of sterile ophthalmic solutions, noting specific deviations including the failure of management to ensure that an effective Quality System has been implemented and maintained at all levels of the organisation; failure to establish procedures for identifying training needs and ensure that all personnel are trained to adequately perform their assigned responsibilities and to document such training as required by 21 CFR 820.25(b). FDA specifically noted the range of training deficiencies, identifying inadequate or nonexistent training for the company’s QA/QC/RA Manager, the VP/Operations Manager, the firm’s microbiologist technician, and the individual charged with quality assurance testing on the product’s raw material.

Assuring Consistent Compliance

Each medical device manufacturer experiences unique conditions, product requirements and staffing needs. Despite those variations, all medical device manufacturers are held to a specified standard of compliance. Achieving and maintaining that compliance is not a choice; it is a basic business requirement that requires committed actions including the following:

1. Development of Standard Operating Procedures to ensure compliance with all regulated activities;
2. Distribution of all relevant information including protocol and production changes, corporate codes of conduct, SOPs, and regulatory advisories. Receipt of all information by responsible parties must be validated.

Committed Actions for Achieving and Maintaining Compliance:



3. Documentation of all compliance activities including information distribution and validation, training, and corporate communications with employees;
4. Assurance that all responsible parties – subcontractors, vendors, employees, senior managers and corporate executives – have the necessary knowledge to fulfill their job responsibilities. Simply “providing training” is inadequate to meet compliance; responsible parties must be able to apply the required knowledge in compliance with regulatory requirements.

As with the Directives issued by the European Commission, the regulatory requirements of the FDA are designed to assure patient safety while providing access to the most effective medical technologies available. The complexity of regulation is likely to increase, rather than decrease, as new areas of research introduce innovations in tissue engineering, nanotechnology and combination products. Given the commitment of global regulators to harmonize standards and regulatory requirements, the challenges of compliance in the US may shrink. Until then, access to the world’s largest medical device market is governed by the requirement to comply with regulations that echo other national and international commitments to patient safety but that remain unique – and that require responses tailored to achieve compliance effectively and cost-efficiently.

About EduNeering

EduNeering (www.eduneering.com), a Deloitte Technology Fast 500 Company, develops technology-enabled knowledge solutions for improving business performance and assuring regulatory compliance.

For more than 25 years, the company has served corporate and government clients in the life sciences, healthcare, energy and industrial sectors using proprietary platforms that integrate business, learning and technology. Additionally, EduNeering maintains several unique partnerships with its clients, including a Cooperative Research and Development Agreement with US Food and Drug Administration.

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