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Medical devices and supply companies are under enormous pressure to fulfill trade requirements dictated by current global markets, especially by the EU, although it is largely recognized that the innovative medical devices and procedures can considerably improve diagnostics and shorten therapeutic cycles. There are more than 8000 generic medical device groups where some devices contain drugs. The EU increases the demand for better regulatory frameworks to ensure that products entering the market are safe and efficient, even if they are essential for people's health and quality of life, and the industry that provides them plays a significant role in the economy. New treatment methods and innovative products are not easy to position in the EU market, and for this reason, one of the major issues for companies developing and producing medical devices is to be updated on the regulatory requirements and implement them.

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Introduction

Medical devices and supply companies are under enormous pressure to fulfill trade requirements dictated by current global markets. Simultaneously, the medical devices become even more important in the health care sector, because innovative medical devices and procedures can considerably improve diagnostics and shorten therapeutic cycles. Against this backdrop, international standardization of products and prices, entry into emerging markets, product bundling and integrated treatment solutions are gaining in importance. For the moment, there are more than 8000 generic medical device groups where some devices contain drugs. This is the main reason why the EU increases the demand for better regulatory frameworks to ensure that products entering the market are safe and efficient, even if they are essential for people's health and quality of life, and the industry that provides them plays a significant role in the economy. New treatment methods and innovative products are not easy to position in the EU market, and for this reason one of the major issues for companies developing and producing medical devices is to be updated on the regulatory requirements and implement them in the process. Besides, providers wishing to stand out from the competition need creative strategies, quality marketing, targeted branding and customized service. All of them have to develop and implement best-in-class operating models that help them outperform the market.

1. Defining the medical devices

According to the European Union³¹⁷ definition, “Medical devices are [...] articles which are intended to be used for a medical purpose. The medical purpose is assigned to a product by the manufacturer. The manufacturer determines through the label, the instruction for use and the promotional material related to a given device its specific medical purpose. As the directive aims essentially at the protection of patients and users, the medical purpose relates in general to finished products regardless of whether they are intended to be used alone or in combination. This means that the protection ensured by the directive becomes valid for products having a stage of manufacture, where they are supplied to the final user. Following this concept, raw materials, components or intermediate products are as such normally not medical devices. Such raw materials may need to present properties or characteristics which are determinant for the safety and quality of finished devices. It is therefore the responsibility of the manufacturer of finished devices to select and control by adequate means his raw materials or intermediate products”.

The concept of "finished device" does not imply that a device when reaching the final user is already in a state ready for use. Prior to use further preparatory processing, preparation, configuration, installation, assembling, adaptation or fitting to the needs of the user or patient may be required. Examples:

- sterilisation of medical devices supplied non-sterile;
- assembling of systems;
- configuration of electronic equipment;
- preparation of a dental filling;
- fitting of contact lenses;
- adaptation of prosthesis to the needs of the patient.

The aforementioned activities are normally not manufacturers' activities if they are carried out by the final user as part of the use or preparation for use. In this context a distinction needs to be made between a typical professional activity performed by a healthcare professional and processing and assembling activities done by a specialist for such processing.

The definition of the term "medical device" together with the definition of "accessory" is determinant for the delimitation of the field of application of Directive 93/42/EEC. A slight difference exists between the definition in article 1(2) (a) of Directive 93/42/EEC and in article 1(2) of Directive 90/385/EEC.

Following the latter directive, accessories are by definition medical devices, whilst following Directive 93/42/EEC, a distinction is made between "devices" and "accessories". Therefore within the meaning of Directive 93/42/EEC, accessories are products in their own right and, although being treated as devices (article 1(1)) do not follow, as a general rule, the classification of related devices in conjunction with which they are used. Accessories are therefore following Directive 93/42/EEC to be classified in their own right.

This means that medical devices are everything from band aids to x-ray machines, contact lenses, hip implants, pacemakers, crutches, hospital beds and in vitro diagnostic devices.

Medical devices are usually divided into subgroups. In Europe medical devices are divided into three different groups; active implantable medical devices (AIMD), general medical devices and in vitro diagnostic devices (IVD). These groups are recognized and used by other countries as well. The main difference between countries is how these devices are regulated. In some countries medical devices are regulated as drugs and in other countries there are special regulations for medical devices (Brolin, 2008). Medical devices can in turn be regulated as one

317 EUROPEAN COMMISSION, DG ENTERPRISE, Directorate G, Unit 4 - Pressure Equipment, Medical Devices, Metrology, MEDICAL DEVICES: Guidance document, MEDDEV 2. 1/1, April 1994, available at http://ec.europa.eu/enterprise/medical_devices/meddev/2_1-1___04-1994.pdf, last consulted on April 5th, 2009

group or regulated separately, usually as one of the subgroups. In Europe general medical devices are divided into non invasive devices, invasive devices and active devices. An active medical device is a device that requires a source of energy to function. An invasive medical device is a product that in some way enters the human body. The device is then called invasive, surgically invasive or implantable depending on how the device is entering the body and the time it is introduced to the body. An in vitro diagnostic device is a reagent, reagent product, instrument or system used to examine samples from human tissues or fluids to gain information. In vitro diagnostic devices are also divided into subgroups (Landvall, 2007).

When it comes to the *classification of the medical devices*, they are usually divided into different classes. Some countries have separate classification systems for general medical devices, active medical devices for implantation and in vitro diagnostic devices while other countries classify these products after the same system. All classification systems are risk based. Classification of medical devices is necessary to apply correct regulations and quality systems (Brolin, 2008).

In the United States medical devices are classified as class I (General Controls), II (Special Controls) or III (Pre-market Approval) devices where class III devices represent the highest risk and require more control. Medical devices are classified through a classification database found at the FDA homepage and are given a seven digit number based on the product category (9).

In the European Union general medical devices are classified as class I, class I sterile, class I measuring, class IIa, class IIb or class III where class III devices represent the highest risk. Active implantable medical devices are not classified and in vitro diagnostic devices have their own classification system. Information on the European classification system is found in MEDDEV 2.4/1. The classification rules are found in Annex IX of Directive 93/42/EEG (Landvall, 2007).

The Global Harmonization Task Force (GHTF) described further down has developed a recommended classification system where medical devices are divided into class A, B, C and D where class D represents the highest risk. This system is however a recommendation to regulatory authorities and not to companies. Information on the GHTF recommended classification system is found in the GHTF document "Principles of Medical Devices Classification" (Brolin, 2008).

A nomenclature is usually given to a medical device when it is classified. There are two international nomenclatures that are very common:

- *The Emergency Care Research Institute* (ECRI) nomenclature called the Universal Medical Device Nomenclature System (UMDNS). The UMDNS terms are harmonized with the classification system of the USA and exist in ten languages (2).

- *The Global Medical Device Nomenclature* (GMDN) codes. The GMND code is built according to EN ISO 15225 and is collaboration between the EU, EFTA, USA and Canada (6). The GMDN terms only exist in English but can be translated with special software. This nomenclature system is required for registering a medical device within the EU (8).

Both systems consist of defined terms that describe a group of products with similar characteristics. The GMDN system is developed from 6 different nomenclature systems and the UMDNS system is one of them. GMDN and UMDNS harmonize with each other but GMDN has more terms and is therefore preferred (10).

2. Quality Management Systems

Manufacturers of medical devices need to apply suitable quality systems for their products. The requirements differ on the risk of the device and are usually dependent on the product class.

Good Manufacturing Practice (GMP) is the most common requirement but there are also other quality guidelines (GXP's). There is Good Clinical Practice (GCP) describing quality requirements for clinical trials, Good Laboratory Practice (GLP) describing quality requirements for laboratories and research organizations to ensure consistency and reliability of results, Good

Distribution Practice (GDP) for proper distribution of medical products and Good Vigilance Practice (GVP) (Brolin, 2008).

These guidelines and several others have been established by International Conference of Harmonization (ICH) and have been adopted by USA, EU and others. Most countries have their own variations of the guidelines and these are usually found at the homepage of the competent authority.

The International Organization for Standardization (ISO) has developed a standard for quality management system for medical devices called ISO 13485. This standard is based on ISO 9001:2000 and helps companies implement and maintain a quality management system. This standard is by many countries recognized as a way to reach Good Manufacturing Practice. The most important medical device standards concern biocompatibility ISO 10993, clinical trials ISO 14155 and risk management ISO 14971. Active medical devices are also subject to ISO/IEC 60601 and medical devices including software are subject to IEC 62304 (Landvall, 2007).

3. Regulation of Medical Devices

Manufacturers of medical devices need to adjust to the regulatory framework in the country where the product is sold. This constitutes a great problem for manufacturers, especially for companies selling their products in several countries. Competent authorities worldwide have begun to realize the problem and collaborate to harmonize the regulations (Brolin, 2008).

The Global Harmonization Task Force (GHTF) is a group of representatives from regulatory authorities in USA, European Union, Japan, Australia and Canada that work to harmonize the regulations for medical devices and improve the safety, effectiveness and quality of the devices. The group has developed guidelines for pre-market evaluation, post-market surveillance, quality systems, auditing and clinical safety/performance. Many countries have begun to adopt these guidelines or follow the United States Food and Drug Administration (FDA) regulations or the European Medicines Agency (EMA) regulations. Medical device requirements are basically the same in most countries but are implemented in different ways (5).

USA

The FDA regulates food, drugs, medical devices, biologics, cosmetics and radiation emitting products in the USA. FDA's Center for Devices and Radiological Health (CDRH) is responsible for regulating manufacturers of medical devices. Medical devices are regulated under the Federal Food Drug & Cosmetic Act (FD&C Act) Part 800-1299 (Brolin, 2008).

Manufacturers importing medical devices into the USA must designate a United States agent, register the establishment, list the device, manufacture according to the quality system requirements and file a Premarket Notification 510 (k) or a Premarket Approval. A post marketing surveillance system is required (21 CFR Part 803). Medical devices are divided into Class I, Class II and Class III where class I devices represent the lowest risk and class III devices represent the highest risk. Most Class I devices and some Class II devices are exempt from a Premarket Notification 510 (k). Class II devices generally require a 510 (k) while Class III devices require a Premarket Approval. Devices shall be given a device product code consisting of two numbers and three letters describing what type of device it is. Regulation for establishment registration and medical device listing is found in 21 CFR 807. The establishment registration shall be renewed once a year and the device listing updated once a year between October 1st and December 31st. Good manufacturing Practice (GMP) shall be applied according to 21 CFR Part 820 (Brolin, 2008).

Some devices of Class I are exempt from GMP requirements (9). The international standards for risk management ISO 14971 and biocompatibility ISO 10993 are accepted (10).

European Union

The European Medicines Agency (EMA) is a decentralized body of the European Union (EU) whose responsibility is to protect human and animal health through the evaluation and

supervision of medical products for human or animal use. This information is found at the EMEA homepage. Medical devices are subject to Directive 93/42/EEG and must be CE-marked before entering any country in the EU. Active implantable medical devices are subject to Directive 90/385/EEG. Manufacturers of drugs and medical devices who want to sell their product to a country in the EU only submit one single marketing authorization application to the EMEA. The documentation shall be written in English, French or German. A manufacturer that does not have a registered place of business in the EU shall designate a single authorized representative in the European Union (Brolin, 2008).

Medical devices are divided into class I, class IIa, class IIb and class III where class I also have the subclasses sterile and measuring. The devices shall have a GMDN code. All medical devices exempt class I devices require the involvement of a Notified Body. Medical devices and their accessories are treated as medical devices. Medical devices must meet the essential requirements in Annex I of Directive 93/42/EEG. Standards are used to meet and demonstrate compliance with the essential requirements. Manufacturers of medical devices must have a quality system (4). ISO 13485 is normally used (Landvall, 2007). Clinical trials are required for active implantable devices, class III devices and invasive devices for long-term use of class IIa and IIb. Instructions for use are not necessary for class I and IIa devices if they can be used safely without them. A registration of a product is valid for five years (4).

4. Discussion

EU and USA have similar requirements for registration of medical devices and are striving to harmonize their requirements with the GHTF guidelines. A company can go far by following the requirements of the European Union, USA or GHTF.

The main requirements are usually a local representative, a Certificate of Free Sale from the country of origin, import license from the competent authority in the import country and registration of the company and the product. To accomplish this it is necessary to fulfill the essential principles, classify the product, apply Good Manufacturing Practice and risk management, follow the labeling requirements and establish a documented post market surveillance system (Brolin, 2008).

Technical documentation is also necessary and shall in most cases be submitted with the registration application. This is where the requirements differ. The essential principles are mainly the same in the countries examined but there are some differences and therefore it is necessary to look at these requirements country by country.

The requirements on risk management for medical devices vary depending on the classification of the device. ISO 14971 is sometimes a requirement or as in most cases a recommendation. Clinical trials are required for more high risk devices. The devices that require clinical trials are about the same in all countries. Special requirements can be that the clinical trials must include people of the nationality of the country of interest. Labeling requirements are generally the same. The language shall be adjusted to the country where the product is sold. Instructions for use are not always necessary depending on the class of the device. Class I devices and sometimes class II devices (depending on the classification system) do not always require instructions for use if the device can be used safely without it.

A documented post market surveillance system is necessary for all medical devices. The main difference here is the responsibility of the sponsor and the manufacturer. The time for maintaining distribution records varies between two years and five years or the product's life time. In extraordinary cases, the time is longer. A company must be aware of the timeframes of the registration process in different countries. This kind of thinking and strategic planning saves time and money (Brolin, 2008).

Concluding remarks

USA and EU have similar requirements for registration of medical devices and are striving to harmonize with the GHTF guidelines. Classification of medical devices is usually done in accordance with the EU system, FDA system, GHTF guidelines or by catalogue. The nomenclature is UMDNS codes or GMDN where GMDN seems to be the most common variant. Main requirements are a local representative, a Certificate of Free Sale from the country of origin, import license from the competent authority in the import country and registration of the company and the product.

Quality management systems and risk management systems are both in USA and EU required, except for medical devices class I. Certificates of ISO 13485 and ISO 14971 are required or recommended.

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