The Medical Device Regulatory System And Patient Safety

Introduction

Over the past two decades, a huge number of new technologies and applications have been introduced in medical practice, opening up amazing possibilities for diagnosis and therapy, but also raising questions of appropriateness, safety and effectiveness. The pace of activity, and the accelerated development in this field, is often on the basis of an uncontrolled diffusion and use of medical technology, as well as of a non-critical acceptance of new technologies. Additionally, the problem of the rising cost of health care, partly resulting from the new technological applications, is perhaps the most pressing issue for many governments today. This situation is expected to continue and by the year 2020, advances in biosensors, molecular and cell engineering, artificial organs, but also in more traditional areas like signal processing, imaging modalities and application of telematics, will change the shape of health care. Increasing cost and sophistication of biomedical technology inevitably leads to an enhanced need for regulation and risk monitoring. Patient and user protection should not be compromised; but this should be achieved without inhibiting progress.

The global market for medical-technology products (excluding pharmaceuticals) was estimated at about $180 billions in 2002, with the European sharing more than 1/3 of this world market. Fragmentation of the European market, however, due to inconsistencies in national regulations which have imposed technical, physical and financial barriers, hasn't allowed European manufacturers to take full advantage of this wide market. In order to remove these internal barriers and facilitate the free movement of goods, the EU has adopted the "New Approach" on technical harmonization. Under this new framework, the Commission is working on harmonized, community-wide legislation which, in the medical device sector, is addressed by means of three directives: the Active Implantable Medical Device (AIMD), the Medical Device (MD) and the In Vitro Diagnostics (IVDs) Directive. The EU medical device legislation covers a large range of products. It relates to electromedical equipment, surgical instruments, implants, single-use products, reagents for in vitro diagnosis, laboratory equipment for clinical laboratories, etc, to mention some of the most important product groups which are covered by the term "medical device". Therefore, it has to address correspondingly a range of various risks typically related to medical devices. The relevant EU directives govern the placing on the market of products not only within the 25 Member States of the European Union but in practice the whole European Economic Area including Norway, Iceland, Switzerland, as well as all associated and connected countries.

The "New Approach" And The "Essential Requirements"

The ultimate aim of the harmonization process has been to introduce a set of common rules throughout the EU under which medical devices would be sold and used, thus creating the right conditions for a single market. This policy influences positively the European medical device manufacturers or their authorized representatives established in the Community, by allowing the free movement of products across national barriers. Most of these barriers existed as a result of national laws and regulations concerning the safety of products. In order to lift these barriers, the European Community introduced the application of directives, a set of community legal acts, enacted by the Council of Ministers, which oblige member states to harmonize their national regulations and administrative measures to the requirements of the directives. Under the "New Approach" scheme for the implementation of these Directives, each member state has to nominate Competent Authorities (CA) which, in turn, designate Notified Bodies (NB). According to the "New Approach":

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- Directives should contain Essential Requirements (ERs) with which products must comply.
- Detailed technical provisions will be contained in the harmonized standards adopted by the European Standards organization (CEN and CENELEC).
- Standards are voluntary, but a product that conforms to them is presumed to comply with the corresponding ERs.

A product which complies with the requirements of a directive, is in free circulation, i.e. authorities of a Member State may not stop its entry into the country under normal circumstances. Today all medical devices to be placed on the EU market must bear the CE-mark. This mark is also important in the context of mutual recognition. Mutual recognition means that all Member States of the European Union as well as the EFTA countries must accept the products into their markets and will be required to allow CE-marked products to circulate freely throughout these markets.

The general rule is that medical devices may only be placed on the market and put into service if they do not compromise the safety and health of patients, users and third persons. According to this general rule the manufacturer must:

- Eliminate or reduce as far as possible, the risks associated with the use of the device, in order to obtain safety of the design itself, and
- Provide other appropriate protection mechanisms and measures (for example alarms) when some risks that cannot be eliminated.

Typical risks addressed in specific essential requirements relate to chemical, physical, mechanical, microbiological properties, biocompatibility or emission of radiation. Special emphasis is also put on the information provided with a device and its labelling. If in spite of the above mentioned measures additional residual risks exist, patients and users shall be informed properly through the label and instructions of use accompanying the device. It is therefore obvious that the essential requirements for medical devices require a risk analysis to be performed by the manufacturer. In general any risk, which may be associated with the use of the device, should be acceptable when compared against the benefit expected from the use of the device to the patient. The manufacturer must document how he has proceeded with his risk analysis and which results he has achieved. In practice, the manufacturer must be able to demonstrate that the product complies with the ERs. A product which complies with the ERs and which has followed the appropriate conformity assessment procedure is marked with a CE mark, which is its passport for free circulation throughout the European Union market.

The Medical Devices Directives

As mentioned before one of the first fields of application of the "New Approach" is the medical technology one, covered by three separate directives. The first directive on Active Implantable Medical Devices (AIMD) was adopted in 1990 and came into force in the form of national legislation in 1993[1]. The AIMD Directive applies only to a small number of devices, which are implanted (partially or totally) in the human body and where their functionality relies on the existence of a power source (i.e., infusion pumps, pacemakers, implantable drug pumps neurostimulators, cochlea implants, etc). The directive contains essential safety requirements, mainly dealing with sterility, protection of patients against risk of physical injury, or hazards related to the use of electricity, etc. The real technical details were to be included in the harmonized European standards published by the European standardization organizations CEN and CENELEC.

The second directive on Medical Devices (MD) was approved by the European Parliament in 1993 [2]. The MD Directive has become effective since January 1995 and has a transition period until June 1998. After this date, the CE mark becomes mandatory and all medical devices should comply with the new requirements. It is estimated that this directive covers about 80% of the medical devices available today on the market. The MD Directive contains

the essential requirements concerning safety and includes a set of rules for the classification of the medical devices in four classes (I, IIa, IIb, III) as well as the conformity assessment procedures specific to each class.

The third directive relates to In Vitro Diagnostics (IVDs), intended for in vitro analysis of human samples. It is the first time that a single legislation regulates in Europe reagents, as well as equipment, intended for in vitro diagnosis [3]. The in vitro diagnostic medical devices directive has been adopted in 1998 and will become fully applicable by the end of the year 2003.

The cornerstone of all three medical devices directives is the definition of "medical device" which is common to all three directives. A medical device according to Article 1 § 2a) of the medical device directive 93/42/EEC is defined as follows:

"*Medical device means any instrument, apparatus, appliance, material or other article, whether used alone or in combination, including the software necessary for its proper application intended by the manufacturer to be used for human beings for the purpose of:*

diagnosis, prevention, monitoring, treatment or alleviation of disease,
diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap,
investigation, replacement or modification of the anatomy or of a physiological process,
control of conception,

and which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means."

Medical devices are articles intended to be used for a medical purpose. The medical purpose is assigned to the products by the manufacturers. The manufacturer determines the specific medical purpose of a given device through its label, its instructions for use and the promotional material related to this device. The medical purpose relates in general to finished products regardless of whether they are intended to be used alone or in combination. Therefore, the protection ensured by the directives becomes valid for products having a stage of manufacture, where they are normally supplied to the final users. The medical purpose may be achieved either by using a product alone or by using a medical device in combination with other medical devices or other products (e.g. infusion pump used together with necessary tubing and needle). Therefore the manufacturer has a choice to place a product on the market either as a complete system or he may follow the requirements of the directive for different subsets of a system, which can be placed on the market as medical devices, in their own right.

Harmonized Standards And Conformity Assessment Procedures

European standards are elaborated and adopted by the European standards bodies CEN and CENELEC. European standards remain of voluntary character. Therefore the manufacturer is free in his choice, whether he wants to apply relevant European standards or whether he prefers to fulfil appropriate legal requirements by other means than complying with standards. Respecting relevant European standards, however, gives an important advantage to the manufacturer: Certification Bodies and Competent Authorities are in accordance with the directive and obliged to presume compliance with the directives, as far as the manufacturer has met the relevant requirements of the European standards (Article 5 AIMD, MDD). Therefore, respecting the relevant European standards provides for a presumption of conformity with regard to legal requirements. Currently, hundreds of European standards are under elaboration by CEN and CENELEC. Standards which have their reference published in the Official Journal have obtained the status of harmonized standard, and compliance with them creates the presumption of conformity.

The fulfilment of essential requirements and of requirements relating to the design and manufacture of medical devices needs to be established through the so-called "conformity

assessment procedures". It is the task of the manufacturer who places the medical devices on the market to conduct the pertinent conformity assessment procedure in accordance with the directives. By affixing a CE-marking on each medical device, the manufacturer confirms that he has met all requirements of the directive and that he has correctly followed relevant conformity assessment procedures. The details of conformity assessment procedures were adopted in 1990 and reconfirmed in 1993 by the decisions of the Council of Ministers, which lay down eight typical procedural modules for the conduct of conformity assessment. These modules have been used in the meantime in different EC directives governing various sectors such as machinery, personal protective equipment, telecommunication equipment, pressure vessels, etc. The use of conformity assessment modules allows a graduated approach in determining the extent to which an independent certification body has to intervene during the conformity assessment procedure. According to the MDD, medical devices are classified in relation to the potential hazards associated with their use. Depending on the class assigned to each device, the corresponding conformity assessment module(s) that should be followed, are less or more rigorous.

Classification

The classification concept is based on a general risk analysis approach, which estimates potential hazards related to the use of the device, under normal conditions or possible failures. The classification criteria applied take into account of whether a device comes into contact with the human body, if it is invasive, for how long it is used, whether it is used in contact with vital organs such as the heart, or the brain, and if it is activated by an energy source, etc. According to this system, medical devices are classified into:

Class I – Lowest level / Responsibility for compliance lies with the manufacturer
Class IIa – Mainly control of production
Class IIb – Both design and production control
Class III – Highest level / Pre market approval

The responsibility of classification of medical devices rests with the manufacturers who must group their products into the above four classes, in accordance to rules stated in annex IX of the MD directive. Additionally, in order to help manufacturers to classify their products, the Commission of the European Union has issued guidelines to the classification of medical devices into one of the four risk classes using a decision tree [4]. The rules are based on criteria related to duration of contact between the device and the patient, the degree of invasiveness, as well as the anatomy affected by the use of the device. A medical device is classified as invasive, if it penetrates inside the body, either through the surface of the body or through a body orifice. For the non-invasive devices an important classification criteria is contact with blood. Modification of the biological or chemical composition of blood increases the risk associated with a device. Active medical devices are defined as those that are driven by electrical energy and are differentiated in terms of the amount of energy that they exchange with the body.

According to the Medical Device Directive and the Guidelines, the classification rules are applied in accordance with the intended use of the device and not its particular technical characteristics. It is, however, possible that a manufacturer would assign a different intended use to a product, than another manufacturer producing a similar device. Therefore the intended and not the accidental use of a device is regarded in the determination of the class of the device. If a user uses a device in a manner not intended by the manufacturer of the product, this is done under its own responsibility and does not change the class assigned for the conformity assessment procedure. Whenever there is a doubt over the classification resulting from application of the rules of the Medical Device Directive, the manufacturer should address the question to a notified body. In case the manufacturer and the notified body responsible for the conformity assessment have a dispute on the application of the classification rules, the manufacturer should refer the matter to the competent authority,

according to Art 9 of the Directive, which will reach a decision. The final body for decision in an extreme case, according to the Directive is the Medical Device Committee.
Conformity assessment procedures, as mentioned previously, are the procedures that must be completed by a manufacturer before the CE-marking can be affixed on a product and a product placed on the market. It is not feasible in practice to subject all medical devices to the most rigorous conformity assessment procedures available. A graduated system of control is more appropriate. A medical device classification system is therefore needed, in order to channel medical devices into the proper conformity assessment route. For devices of class I (simple dressings, corrective glasses, operation tables, and wheelchairs), conformity assessment falls within the entire responsibility of manufacturers. The manufacturer has to examine the compliance of devices with essential requirements. By means of a risk analysis he has to establish whether risks present are acceptable, bearing in mind the intended benefits of devices. For products of this class the manufacturer has to maintain technical documentation and, before placing the product on the market, he has to draw a declaration of conformity that is available to Competent Authorities upon request.

In the case of products of class IIa (syringes, contact lenses, dental filling materials, hearing aids), the manufacturer is responsible for the conformity assessment during the design stage of devices. However, regarding the manufacture of devices he needs to rely on an independent certification body (Notified Body). Products of class IIb (implants, intraocular lenses, X-ray equipment, anesthesia machines and ventilators, high frequency surgical equipment;) and III (heart valves, resorbable implants, medicated devices) are subject to certification by a Notified Body in view of both the design and the manufacturing stage. For class IIa, IIb and III devices, where a third party intervention is required, the manufacturer may always choose between at least 2 alternatively applicable procedures; basically between the certification of products or the certification of his manufacturing system. In the latter case the continuous running of the manufacturer's quality system is subject to a third party certification by a Notified Body. In this context compliance with pertinent European standards (series EN/ISO 29000 in conjunction with EN 46000) facilitate the establishment of conformity.

The Medical Devices Regulatory Framework In The USA

The FDA regulation for marketing devices differs on the basis of their potential risk. Devices are classified, following recommendations from FDA classification panels, into three classes:

- Class I contains devices for which general controls are sufficient to provide reasonable assurance of safety and effectiveness (for example: elastic bandages, examination gloves).
- Class II encompasses devices which cannot be classified in Class I, and for which special controls, which might include special labelling requirements, mandatory and voluntary performance standards and post-market surveillance, are required (for example: X-ray devices, infusion pumps)
- Class III applies to devices that cannot be classified in Class I or II and that support life, prevent health impairment, or present a potentially unreasonable risk of illness or injury, like cardiac pacemakers.

Unless exempted, manufacturers must register their devices with the FDA. The faster marketing process is the Pre-marketing Notification, 510(k), under which the manufacturer has to demonstrate that the device to be marketed is substantially equivalent to a legally marketed device that is not subject to PMA, in order to prove safety and efficacy. The notification has to be submitted to FDA at least 90 days before starting to market the device. If FDA finds that the device is not substantially equivalent to one already in use, then the device must go through a Pre Market Approval (PMA) process, which is the most stringent type of device marketing application required by FDA. As a result, the device is also automatically classified into Class III. The PMA process requires valid scientific evidence to be provided by the manufacturer, in order to prove safety and effectiveness for the device’s intended use(s). All clinical evaluations of investigational devices must have an approved investigational device

exemption (IDE) before the study is initiated. This allows the limited use of the investigational device in a clinical study in order to collect safety and effectiveness data required to support a PMA or a 510(k) submission to FDA.

The European Medical Devices Vigilance System

One of the most important tasks under the "New Approach" is the implementation of vigilance procedures concerning medical devices. The regulations covering medical devices concentrate primarily on pre-marketing requirements, but do not always ensure that the products will be either safe or effective during their use. From the perspective of the health care facility, a medical device should, whenever appropriate, be subject to continuous monitoring and quality control of its functional status in the post-marketing life cycle. On the other hand, the responsibility of the manufacturers should not stop when the device is put on the market. They must also encourage the correct application of their products through appropriate guidance or user training and monitor that their performance is according to their specification. Early warning of unexpected adverse effects can be obtained by the users, either by reporting back to the manufacturers (Post Market Surveillance), or to the competent authorities (User Reporting System), for any deviation of the devices expected performance. Post Market Surveillance may be of an extreme importance for the manufacturer, with respect to obtaining feedback from the users, in order to continuously improve reliability. The EU Directives contain some provisions regarding Post Market Surveillance. Obligations rest especially with manufacturers who should institute and keep updated a post market surveillance system (incident-reporting and recalls). The AIMD Directive contains requirements for reporting device incidents. Instead of the term Post Market Surveillance System, in the MD Directives there is provision for "a systematic procedure to review experience gained from devices in the post production phase and to implement appropriate corrective action" that the manufacturers have to comply with.

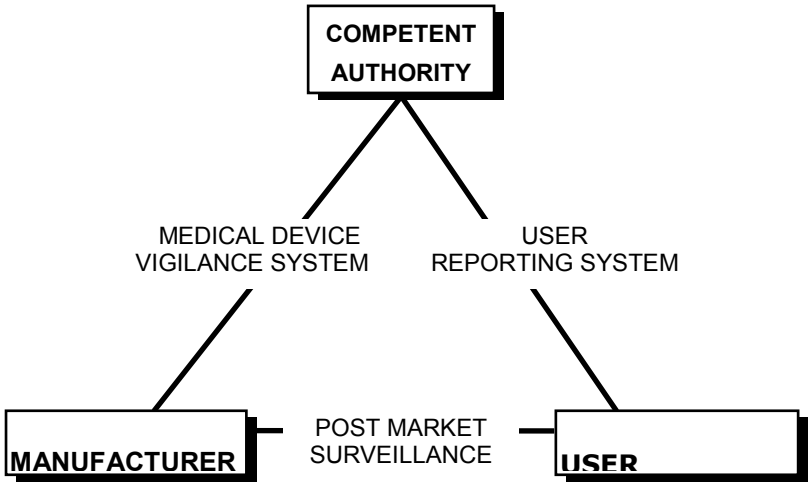

Figure 1: Schematic diagram of the parties involved in the MDs vigilance procedures

Even if the manufacturer is assigned with such a task, the follow-up of maintenance schemes remains the responsibility of health care facilities and care professionals. The health care facility should make the necessary arrangements for ensuring that devices are maintained and used properly. However, there is no reference in the directives formalising this responsibility. Member States are responsible for introducing appropriate measures in the framework of ensuring quality assurance and meeting the user's safety requirements.

According to the Directives, every Competent Authority in the European Union must implement a user reporting system in order to assure that adverse incidents involving medical devices are

properly investigated, and the appropriate measures are taken in order to prevent reoccurrence. On the other hand manufacturers are also legally obliged to report any serious incidents, death or serious injury, involving a device they produce and sell. Based on these requirements, the Commission has prepared an adverse incident notification and evaluation system in the form of the Medical Devices Vigilance System Guidelines [5]. The aims of the Medical Device Vigilance System are:

- To prevent the reoccurrence of incidents with the same type of medical devices, at another place, at another time
- To encourage manufacturers to perform investigation and take corrective actions if necessary
- To enable the superior authority to monitor the investigation procedures and intervene when necessary.

Although the Guidelines are voluntary and do not have the status of a law, they provide guidance in the application of the requirements of the directives, helping the transposition of the directives into national laws, as well as the implementation of the necessary structures. Under the Vigilance System Guidelines, reports should be submitted by the manufacturer to the Competent Authority, in the country where the incident occurred. Manufacturers must notify the concerned Competent Authority of an incident within 10 working days when death has occurred, or within 30 days for all other incidents, by completing a specially designed initial report form. This period is initialized when the manufacturer is first informed of the incident and is completed when the relevant Competent Authority receives notification from the manufacturer. Each initial report is evaluated by the relevant Competent Authority and when necessary follow up actions are undertaken.

Generally, manufacturers are encouraged to perform investigations and, if necessary, to take corrective actions. The Competent Authority should monitor the manufacturer's investigation and intervene, if necessary. At the end of the investigation any information necessary for the prevention of further incidents (or the limitation of their consequences) should be disseminated in the form of a final report to all other Competent Authorities and the Commission. Exchange of information between member states is necessary mainly when measures have to be taken, or envisaged, as a consequence of an incident report. In case of a recall, the responsible Competent Authority should ensure that information is given in such a way that there are no negative effects on anyone involved.

Confidentiality is also an important issue. The initial reports received by a Competent Authority are confidential, but when there is an outcome of the investigation this should be made known to the rest of the CAs, in order to prevent the occurrence of other similar incidents. On the other hand, dissemination of information, which has not been verified, can result in serious negative consequences for both manufacturers and patients, and for that reason special care is required. In order to meet these requirements, most member states have or are in the progress of implementing their national medical device vigilance systems.

Tracking Systems

Although implanted devices receive regulatory approval before clinical use, many of them can create problems when applied to patients, due to poor biocompatibility or to inherent physiological human variability. Furthermore, some devices have a finite performance over time. However, their use should be judged based on the benefits for the patient compared to the risks. It is thus necessary to assess, in many cases, device performance after its application to the patient. Keeping track of where certain devices are, and assessing the clinical outcome constitutes the subject of Tracking Systems, for both patient as well as medical devices. Tracking a device or implant means following the item from the manufacturer or importer to the ultimate user. Device traceability requires gathering of data from manufacturers or importers, distributors, physicians, hospitals, and finally the patients. A great responsibility is placed on manufacturers. The history record of a device reflects product

design, patient life expectancy, device cost, and many other useful parameters. Maintaining a tracking system for implanted medical devices implies that it is possible to have information about the patient, i.e. to be able to have the patient under continuous observation, throughout his life or the device's lifetime and maintain the information in a Patient Registry, respecting confidentiality.

As mentioned previously, the approaches in the field of medical device vigilance in the EU countries, prior to the implementation of the directives, were very different and no formal, commonly adopted communication structure between the involved authorities existed. The medical device directives have imposed new requirements and the need for a harmonized approach and cross-national exchange of information has been recognized. Effective and efficient data handling and exchange tools are required. Evidently, we are currently experiencing the new communication era and it is naturally expected that telematics will provide the appropriate means and tools for an effective, commonly accepted approach in information exchange [6].

Medical Device Software And Safety

The impact of informatics on the medical device sector has increased enormously over the last ten to fifteen years. Software is today either embedded in a wide range of medical equipment, or used as an accessory, or as a standalone medical device in its own right. The evolution of computer technology, in combination with the new advances of software engineering, sustains the high level of progress in the domain. The implementation and integration of software in medical devices is increasing and from this perspective, it becomes critical to face the issue of quality design of the software products, in order to ensure safe and reliable performance and to bring the benefits from their usage right to the patient with minimum risks.

Medical device software safety has recently been revealed as an important issue due to its critical character. A significant number of incidents due to software failures have been reported in the past few years. In fact, software differs dramatically from hardware in many respects. Some of these differences are related to the fact that it is very easy to modify and update without precise control, whereas producing copies is so easy and uncontrolled that makes traceability difficult. Additionally, due to its high complexity, it is generally almost impossible to fully check software for quality/safety. Functional testing of the final product is therefore not an efficient method of quality assurance [7]. The software quality management system should include issues addressing traceability, verification, validation and change control. The whole field of medical informatics is not well regulated. Some products, although critical from patient safety point of view, are not regulated at all. The Electronic Health Record (EHR) and many Decision Support Systems (DSS) fall in this category. The EHR is in fact a complex product consisting of many sub-products. It is also continuously adapted and maintained. It is therefore rather a service that is put on the market, than a single product, and therefore requires a life long quality/safety assurance, regarding its implementation, use and maintenance. Fatal accidents have occurred due to software errors that, for example, have caused wrong patient blood groups, or electronic prescriptions. There are also indications that there is a trend towards an increasing proportion of medical device failures due to software, reflecting the growing importance of software in these products.

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