Regulatory Processes Necessary to Commercialize A Seizure Prediction Technology

Promises and Pitfalls of Biosignal Analysis: Seizure Prediction and Management (A case study);

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Abstract-**This presentation will focus on the regulatory process followed when commercializing technology designed to predict/detect seizures. The author will describe the general requirements required to commercialize implantable medical products in the various regions of world. He will contrast the differences in the requirements for different regions and describe efforts to harmonize those requirements between the European Community and the United States. Furthermore he will identify some of the unique clinical and regulatory issues associated with commercializing a seizure management system incorporating algorithms for processing biosignals to predict/detect seizures.**

1. Introduction

The successful operation of medical device companies is presently affected by their ability to continuously comply to the regulatory requirements applicable in the different areas in the world, such as :

- FDA medical device regulations in USA
- EU medical device directives in Europe
- PHB medical device regulations in Canada
- MHW medical device regulations in Japan
- TGA medical device regulations in Australia
- Others

2. New approach

In line with the EU policy to establish a free trade zone among its Member States, the EU Commission implemented in 1985 the "New Approach" resulting in a new legislative procedure in the European Union (formerly EEC), based on the compliance to Essential Requirements and the use of harmonized European standards.
This new system sets minimum requirements to products for ensuring the necessary level of protection with regard to safety, health and environment.
If the relevant product complies with the applicable essential requirements and the other provisions of the directive, the CE marking can be applied on the device or its packaging /labeling.

3. Medical Device Directives

a. ***Active Implantable Medical Devices (AIMD)***

The directive (90/385/EEC) covers those medical devices, which rely for its functioning on a power supply (e.g. battery) and are implanted in the human body. This directive also covers the parts/ accessories necessary for the proper functioning of the active part.
Examples of AIMD's of Medtronic are :

- IPG's (cardiac pacemakers)
- Implantable Leads
- Lead adapters
- Programmers
- Stylets, etc.

From January 1, 1995 the provisions of the Active Implantable Medical Device Directive are mandatory. This means that all these medical devices require a CE marking before they are placed on the market.

b) ***Medical Device Directive (MDD)***

The directive (93/42/EEC) covers all other medical devices (Non-Active and active external) and their accessories, which are not covered by the above AIMD directive (except for Article 19, in which amendments of the AIMD directive are given) and the third directive for In Vitro Medical Devices, which is in preparation.
This directive covers a large range of medical devices.
Examples of MDD products of Medtronic are :

- Balloon catheters
- Guiding wire
- Oxygenators
- Heart Valves
- External pacemakers
- Others

The MD directive took effect on January 1, 1995, with a transition period until June 14, 1998.

c) ***In Vitro Diagnostic Device Directive (IVD)***

This directive will cover the medical devices, instruments or systems which are intended to be used in-vitro for examination of substances derived from the human body. This directive will also include amendments of the second directive (MDD)

d) ***Other applicable EU directives***

Other EU directives, which are generally applicable, need also be taken in consideration, such as :

- Directive on liability for defective products
- Directive on Electro-Magnetic Compatibility
- Directive on measuring units
- Directives on environmental pollution and packaging waste

4. Specific Items with the Directives

The following sections of this guide will highlight specific provisions for the implementation of the AIMD (90/385/EEC) and MD (93/42/EEC) directives, and will focus on the requirements for obtaining and keeping the CE marking and what they mean for Medtronic.

a. ***Terminology***

(1) Competent Authority

The Member State Ministry of Health, who is responsible for the public health and order

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Abstract

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(2) Notified Body
Inspection Body(ies) designated by each Competent Authority for carrying out the tasks pertaining to the conformity assessment procedures of the relevant directive.

(3) Placing on the Market
The first making available in return for payment or free of charge of a device with a view to distribute and /or use on the Community market, regardless of whether it is new or fully refurbished

(4) Putting into Service
The stage at which a device is ready for use on the Community market the first time for its intended purpose (by the user)

(5) Intended Purpose
The use for which the device is intended, according to the data supplied by the Manufacturer on the labeling, IFU and /or promotional papers and is CE certified.

b. ***Clinical Investigations***

1. In case of devices intended for clinical evaluation / research, the procedure referred in Annex 6 (AIMD) or Annex VIII (MDD) shall be followed and the Competent Authority(ies) of the Member States, in which the investigations are to be conducted, shall be notified.

2. All clinical investigations on devices covered by AIMD directive and those falling within Class III and implantable and long term invasive devices falling within Class IIa and IIb may commence at the end of a period of 60 days, unless the approval have been received earlier

3. Clinical Investigations / Devices
If no clinical evidence of a new product or its intended use or material or technology is available, a clinical investigation has to be performed. For the clinical investigation the following main requirements are applicable :

- With the Notification a statement must be included, stating the compliance of the device/ system to the relevant Essential Requirements
- The clinical investigation has to comply to EN 540, the European harmonized standard for clinical investigations
- Products for clinical investigation shall marked "exclusively for clinical investigation"
- CE marked devices intended for a clinical investigation shall be applied for the intended use as certified, otherwise the CE marking have to be replaced by the marking "exclusively for clinical investigation"

5. Classification

One of the main differences between the AIMD Directive and the MD Directive is the classification system of the MD Directive.
The AIMD Directive covers all parts of active implantable medical device systems which rely for its functioning on a power supply (e.g. battery) and does not distinguish the devices into classes.

The medical devices covered by the MD directive are classified according the classification rules given in Annex IX of this directive as follows :

- **Class I for low-risk devices**
  Examples : Reusable instruments

- **Class IIa for low medium-risk devices**
  Examples : Oxygenators, blood heaters, cannulae, single-use surgical instruments, etc.
- **Class IIb for high medium-risk devices**
  Examples : external pacemakers, blood pump console, etc.
- **Class III for high-risk devices**
  Examples : heart valves, cardiovascular catheters, temp pacing leads, etc.

6. Labelling

Labelling claims are based on clinical justification. Intended use and therapeutic benefit as claimed by the manufacturer is based on clinical outcome. Claims made in the labeling without sufficient prove is considered mislabelling

All member states do have presently the requirement of local language labeling in the laws transposing the Directives in their own legislation. As there is no universal European language (and never will be) the labeling information could take, as far is possible, the form of symbols.

REFERENCES

[1] Council Directive of 20 June 1990 concerning Active Implantable Medical Devices (90/385/EEC).
[2] Council Directive of14 June 1998 concerning Medical Devices (93/42/EEC).
[3] NB-MED/2.7/Rec1, guidance on Clinical Investigations, Clinical Evaluation.
[4] EN 540 Clinical Investigations with Medical Devices
[5] ISO 14155 Clinical Investigations with Medical Devices