

# Clinical Research and Medical Devices in Europe

Alison Welsby, Senior Clinical Project Manager, PharmOlam International Ltd, Ascot, UK



A. Welsby

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## Summary

The term “medical device” covers a huge range of products, everything from contact lenses to heart valves. Widespread formal clinical evaluation of medical devices has only been a feature of past 20 years. However, the well publicised failure of some medical devices has led to the implementation of 3 medical device directives in the European Union. (EU) These were introduced to try to ensure the safety and performance of medical devices available for sale in the EU. Two directives cover active implantable medical devices and *in-vitro* diagnostic medical devices and a third directive, covers all remaining devices.

All devices medical devices for sale in the EU now have to demonstrate minimum standards of safety and efficacy, the so called “Essential Requirements” of the Directives. Once this has been done, the device is allowed to bear a CE mark. The CE mark is not a mark of quality, rather of safety, and denotes that the device is fit for its intended purpose. Once a CE mark has been placed on a device, it can be freely marketed in the European Economic Area without further controls and there is growing acceptance of the medical device directives outside of Europe.

「医療用具」という用語の対象とする範囲は非常に広く、コンタクトレンズから人工心臓弁までの多種多様な製品が含まれる。医療用具の臨床評価が正式に広く認められるようになったのは、わずかこの20年ほどのことである。しかし、数種の医療用具における欠陥が広く報道されたことが発端となり、欧州連合(EU)において医療用具に関する指令が3件発令された。これらの指令は、EU地域において販売されている医療用具の安全性と性能を保証する目的で導入された。2件の指令は、可動タイプの埋め込み型医療用具ならびに体外診断用医療用具をカバーするものであり、3番目の指令は前記以外のあらゆる医療用具を対象とするものである。

現在EU圏内で販売を目的とするあらゆる医療用具は、いわゆる上記指令の「必須要件」と称される安全性ならびに効能に関する最低基準を満たしていることが証明されなければならない。最低基準を満たしていることが証明されると、その医療器具にはCEマークを表示する許可がある。このCEマークは品質マークではなく、むしろ安全性マークであり、この医療用具が意図する使用目的に適していることを意味している。CEマークが医療用具に表示されることにより、欧州経済地域内でその他の制限を受けることなく自由に販売が可能になる。また、ヨーロッパ以外の地域でもこの医療用具に関する指令の採用が広がりつつある。

## Introduction

The term “medical device” covers a huge range of products. It includes contact lenses and condoms; heart valves and hospital beds; resuscitators and radiotherapy machines; surgical instruments and syringes; wheelchairs and walking frames and many thousands of items used each and every day by healthcare providers and patients. To evaluate whether or not a product is a medical device, since there are many grey areas, consideration should be given to the intended purpose of the product taking into account the way it is presented and the method by which the principle intended action is achieved.

In the case of a medical device the principle intended action is typically fulfilled by physical means (including mechanical action, physical barrier, replacement of, or support to organs or body functions). The action of a medicine is typically achieved by pharmacological, immunological or metabolic means.

## Background

Formal clinical evaluation of medical devices is a relatively recent occurrence. Before 1990, there were inadequate and inconsistent regulations governing the safety and efficacy of marketed medical devices both in Europe and the USA. Until 1976, new devices were classified as new drugs in the US so they could come under the jurisdiction of the FDA. However, the well publicised failure of some medical devices caused a public outcry and changes in the regulations governing the sale of devices. Notable cases include:

- The failure of the Bjork-Shiley heart valve which was linked to over 250 deaths <sup>1</sup>
- Silicone breast replacements, some manufacturers had 100% failure rate after 25 years <sup>2</sup>
- Sulzer Hip Replacements (573 patients had to undergo repeat replacement surgery) <sup>3</sup>

## Regulation Changes – Europe

In the European Union (EU), the need to tighten up the regulations covering the sale of medical devices was addressed by 3 medical device directives which were intended to ensure the safety and performance of medical devices in the EU.

Active Implantable Medical Devices Directive – 90/385/EEC <sup>4</sup>  
*This was the first directive to be implemented. Covers all powered implantable medical devices.*

Medical Device Directive – 93/42/EEC <sup>5</sup>  
*This directive enforced from June 1998 regulates most medical devices, for example bandages, condoms and diagnostic X-ray machines.*

The In-Vitro Diagnostic Medical Devices Directive – 98/79/EC  
*This directive regulates products used to examine substances derived from the human body; it came into effect in the UK in June 2000, with a transition period until 7 December 2003.*

## CE Marking

Since June 14, 1998 the CE-Mark is required on medical devices marketed in Europe. The CE-Mark is a proof of compliance with so called "Essential Requirements" of the Directive

MDD 93/42 EEC. The only devices which do not carry a CE mark are custom made devices, devices undergoing clinical investigation, in vitro diagnostic medical devices for performance evaluation. The CE mark is not a mark of quality, rather of safety, and denotes that the device is fit for its intended purpose. Once a CE mark has been placed on a device it can be freely marketed in the European Economic Area without further controls. The EU Medical Device Directive allows manufacturers several options to achieve conformity of product with MDD provisions. Based upon product risk classification, manufacturers can select between several alternative routes of the Conformity Assessment Procedures

Classification of Medical Devices and procedure for obtaining CE marking for high risk devices.

### Classification

Four main classes of device – I, IIa, IIb, III. Class I are the lowest risk devices and class III, the highest.

**Class I** devices are low risk and manufacturers are often self certifying. Examples are stethoscopes, scalpels, hospital beds, wheelchairs. The manufacturer has to produce a technical file, including product test results to relevant standards. In addition, manufacturers of sterile products and devices with a measuring function must apply to a Notified Body for certification of the aspects of manufacture relating to sterility or metrology.

**Class IIa** are low-medium risk devices. Examples include hearing aids, electrocardiographs, ultrasonic diagnostic equipment. Clinical safety prior to CE marking is often demonstrated by reference to other similar CE marked devices.

**Class IIb** are medium-high risk devices. Examples include surgical lasers, infusion pumps (non-implantable), ventilators, intensive care monitoring equipment. Clinical safety prior to CE marking may have to be demonstrated by clinical investigation.

**Class III** devices are high risk. Examples are balloon catheters, prosthetic heart valves. Clinical safety prior to CE marking is usually demonstrated by clinical investigation.

CE marking of new medical devices (class IIb or III) may require clinical investigation if the criteria for 21 CFR 812 (Investigational Device Exemption) are not met. Such devices may employ new materials or components, have no established history of performance or target a new indication or where a significant change in the original intended use of the product is planned. CE marking clinical investigations must meet the minimum acceptable requirements.

### Competent Authority

Each member state has a Competent Authority. The main responsibilities of the competent authority are as follows

- The maintenance of a register of devices manufacturers and the medical devices that they place on the market.
- Ensure only CE marked devices are on the market
- The establishment and administration of a vigilance system for incidents attributable to devices including the withdrawal of unsafe devices

- The examination and approval (if acceptable) of applications for performance evaluation including clinical investigations
- The designation and monitoring of Notified Bodies
- Ensuring that the applicable directives and any modifications are ratified into national law.

#### *Notified Bodies*

Notified Bodies are the only CE marking approval bodies recognised by the European Commission. They are Independent of Competent Authority but appointed by them. Notified Bodies are “notified” (nominated) for the CE marking approval of medium and high risk devices. They often are standards agencies (BSI, TÜV) who are responsible for ensuring a company’s manufacturing procedures are of sufficient quality. They have the power to inspect and audit device manufacturers (conformity assessment) and to check for the implementation of ISO 9000 Quality Control systems.

### Guidelines for EU Clinical Evaluation of Devices – EN540

The clinical evaluation of medical devices is in principle different from the evaluation of pharmaceuticals, for example, for most devices Phase I studies (healthy volunteer) are not an option and obviously the types of evaluation differ there being no true equivalent to dose ranging studies etc. However in practice, the actual process of conducting the study is exactly the same as for pharmaceuticals requiring the same compliance with GCP and any local ethical and regulatory requirements to give data of the highest possible scientific quality whilst protecting the rights of subjects.

To ensure these requirements are met, the EU issued EN540<sup>6</sup> which is a guidance document intended to protect subjects and ensure scientific conduct of medical device investigations in the EU. It is a harmonised document and whilst not compulsory, compliance is usually expected. Its purpose is to help device manufacturers comply with the EU medical device directives. Usually implemented with ICH-GCP which has more specific guidelines regarding clinical investigation particularly relating to statistical analysis of results and the responsibilities of the Investigator and the Sponsor.

Compliance with EN540 alone is not usually sufficient for US regulatory applications. Sole reliance on EN540 by inexperienced sponsors can lead to costly omissions that result in clinical studies lacking in certain key features such as adequate documentation and a sufficiently rigorous statistical analysis plan. EN540 will be superseded Sept 2002 by more detailed guidelines.

### The Scope of Implementation – European Economic Area

The Medical Device Directive (93/42/EEC) is applicable throughout the nineteen Countries of the European Economic Area (EEA).

The EEA is made up of the original 12 European Union member states plus the old 7 EFTA countries (European Free Trade Area). These countries are: Austria, Belgium, Denmark,

Finland, France, Germany, Greece, Holland (The Netherlands), Iceland, Republic of Ireland, Italy, Liechtenstein, Luxemburg, Norway, Portugal, Spain, Sweden, Switzerland, United Kingdom.

All EEA countries accept CE Marked Medical Devices onto their markets, even though they are not all European Union member states. There is growing acceptance of the Medical Device Directives outside the EU.

### Australia

From September 2000 the Australian medical device regulations were harmonised with those of the EU. Only the therapeutic goods administration (TGA) remains as a unique organisation performing pre and post market surveillance.

### Hungary

The Hungarian health ministry intends to publish a new medical device ordinance which transposes the EU medical device directives with a few minor differences. The medical technology bureau (part of the Ministry of Health) will be the competent authority. ORKI (A testing and certification house) has applied for Notified Body status.

### Conclusions

Medical devices are subject to more rigorous pre-market safety testing than ever before. However in a quickly changing environment where advances in healthcare are becoming ever more complex and technological, the regulations governing the safety of medical devices need to be ever more wide ranging and flexible.

Improvements in the safety of medical devices have been the key issue leading to the implementation of the EU medical device directives. The directives achieve this in two main ways.

Firstly, they set a Europe wide, pre-marketing standard for the safety of a device, the so called “essential requirements”, before the sale of that device is permitted.

Secondly, by the establishment of a working vigilance system, devices which fail or are unsafe are quickly identified and their exposure to the market is minimised.

It is hoped that by the implementation of the EU medical device directives that the well documented and appalling device failures of the past will be avoided and that an improved level of confidence in the safety of medical devices will be established.

### References

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**E-mail:** [poi.uk@pharm-olam.co.uk](mailto:poi.uk@pharm-olam.co.uk)

**Website:** [www.pharm-olam.com](http://www.pharm-olam.com)