Role of Medical Device Studies in the Market Authorization Process, Differences and Similarities between USA and Europe

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Abstract: It is often argued that new medical devices are marketed several years earlier in Europe than in the United States of America, as the legislation in the USA is stated to be stricter than in Europe. Basing on this sort of statements, this article takes into account the clinical studies of medical devices that have a key role in the market authorization process. The aim of this article is to make a basic comparison of the clinical study procedures of medical devices for Europe and the USA to provide a general understanding of the similarities and differences of both systems. The basis of both clinical study systems is the risk based classification of medical devices. Building on the similar basic concept, a number of differences are introduced by the two systems.

Key words: Medical devices, clinical investigations, risk based classification.

1. Introduction

In both Europe and the United States of America, the role of Clinical Studies (called Clinical Investigations in Europe) is to verify that the Medical Device (MD) studied provides, under normal conditions of use, the effectiveness (called performance in Europe) it was designed for and the overall risk benefit ratio is favourable. The basis of both systems is the categorization of medical devices in different classes. In general, the classification of medical devices makes a distinction between low, medium and high risk devices.

The intention of the risk classification of medical devices is to apply an accurate level of control required to assure safety and effectiveness of the device.

Another similarity between Europe and the USA is that, for low risk and some medium risk devices, the manufacturers can claim equivalence between their product and the existing product on the market. This way, they need to generate significantly less data on their own product to obtain market authorization.

In spite of it, there are a number of differences between the two systems. To perform this comparison, the current legislation both in the USA and Europe were compared.

1.1 Europe

In Europe, the regulatory framework for the clinical investigations of medical devices consists of three main EC Directives: 90/385/CEE on Active implantable medical devices; 93/42/CEE on medical devices in general; 2007/47 on harmonization of the above EC Directives [1]. These three EC directives have been transposed into the national laws of each EU Member State, resulting in a legislative framework comprised of literally dozens of medical device laws [1].

The European legislation categorizes medical devices into four regulatory classes: Class I, IIa, IIb and III on the basis of increasing risks associated with their intended use.

The need to collect clinical data in the market authorization process (CE marking) arises from the
requirement to demonstrate that a device meets the “Essential Requirements”, namely that it is safe, that it performs as intended by the manufacturer, and that any risks are acceptable when weighed against the benefits of the device.

The evaluation (Clinical Evaluation) of this data must follow a defined and methodologically sound procedure based on:

1. Either a critical evaluation of the relevant scientific literature currently available where
   • there is demonstration of equivalence of the device to the device to which the data relates, and
   • the data adequately demonstrate compliance with the relevant essential requirements.

2. Or a critical evaluation of the results of all clinical investigations made.

3. Or a critical evaluation of the combined clinical data provided by scientific literature and by clinical investigations.

Clinical Evaluation must be based on clinical data not only in the case of implantable devices and devices in Class III (high risk), as planned previously, but for all the medical devices. Every medical device sold in Europe, regardless of its classification, must have a Clinical Evaluation Report in its technical file [2].

Therefore, clinical investigations, as illustrated in Fig. 1, are one of the three pillars of Clinical Evaluation: (1) results of CI; (2) evaluation of scientific literature; (3) combined analysis of data from CIs and from literature.

The first option is commonly used by manufacturers for the CE marking of low- to medium-risk devices (Class I, IIa and IIb) for which safety and performance can be adequately demonstrated by a combination of nonclinical data (i.e., bench testing and animal testing) and clinical data that already exists on the device (published or unpublished) or by analogy with published data generated on an equivalent device. With regard to the high-risk end some medium-risk devices (Class III, IIa and IIb), instead, in the absence of a relevant scientific literature, Clinical Investigations must be conducted.

However, as the objective of a CE marking trial is to demonstrate safety and performance, the majority of these trials are nonrandomized, single arm, and feasibility studies involving less than 100 patients for which the primary objective is to demonstrate safety. In the absence of such specific requirements, the manufacturer must decide which data are sufficient for CE marking (i.e., number of subjects, type of study design, primary and secondary endpoints, type and schedule of assessments, minimum patient follow-up period, etc.). The Notified Body may be consulted with prior to initiating the clinical trial to verify whether or not the protocol is designed to yield adequate data for CE marking.

Moreover, the manufacturer may commence the relevant clinical investigation by simple notification to the competent authorities [3].

In every case, however, it is essential that the relevant ethics committee has issued a favourable opinion on the programme of investigation in question.

The above highlights a key aspect of medical device regulation in the EU. The responsibility for ensuring that devices meet the Essential Requirements (safety and performance) lies with the manufacturer. He is responsible for medical device classification and preparation of Technical File. For low risk devices (Class I) such as a tongue depressor or colostomy bag, the manufacturer is allowed to self-declare conformity with the Essential Requirements. For medium- to
high-risk devices (Class IIa, IIb, III), the manufacturer must call on Notified Bodies, independent companies that specialize in evaluating many products, including medical devices, for CE marks and are designated by Competent Authorities to cover certain types of devices.

1.2 USA

The USA counterpart is the “Investigational Device Exemption” (IDE) established in section 520 (g) of the FD&C Act and in Code of Federal Regulations title 21, part 812 (21 CFR 812) “Investigational Device Exemption (IDE)”. Studies covered under the IDE regulation are subject to differing levels of regulatory control depending upon the level of risk. Precisely, 21 CFR 812 describes three types of device studies: significant risk (SR), non-significant risk (NSR), and exempt studies.

Significant Risk (SR) Device Studies must follow all the IDE regulations at 21 CFR 812 according with them the study may not start until both FDA and the Institutional Review Board (IRB) have given their approval. FDA renders decision within 30 calendar days. In other word, SR Studies must have an IDE application approved by FDA.

Non-Significant Risk (NSR) Device Studies must follow the abbreviated requirements at 21 CFR 812.2(b) according with them the study may start as soon as the IRB reviews and approves the study.

The study may begin without prior approval by FDA. That means that NSR Studies must not have an IDE application approved by FDA.

It’s sponsor’s responsibility to provide the IRB with a risk assessment and the rationale used in making its SR or NSR determination. In this classification, the sponsor is helped by the FDA Information Sheet Guidance “Significant Risk and Non-significant Risk Medical Device Studies”.

An IRB may agree or disagree with the sponsor’s initial NSR assessment. If the IRB disagrees with the sponsor’s NSR assessment and decides the study is SR, the IRB must notify the clinical investigator, and, where appropriate, the sponsor. By the way, if a sponsor or an IRB needs help in making the SR/NSR determination, it may ask for a written determination from FDA [4].

Finally, Exempt Device Studies are exempt from the IDE regulations at 21 CFR 812.

The IRB must still review the study in accordance with the IRB regulations before the study may begin [5, 6]. Exempt Studies are studies of already approved devices used in accordance with their labeling and certain diagnostic device studies. This is illustrated in Fig. 2.

I have focused on SR devices because they must undergo a more exacting and expensive process, requiring clinical trials, known as “premarket approval” (PMA) before they can be sold in the USA.

![fig.2_medical_device_studies_ide_requirements](image-url)
A SR device, by definition, is a device that presents a “potential for serious risk to the health, safety, or welfare of a subject”, i.e. an implant, a device used in supporting or sustaining human life (Class III medical devices) [4].

Clinical studies are required in a PMA application for establishing reasonable assurance of safety and effectiveness. There are essentially two types of IDE studies: feasibility and pivotal studies. The first are studies with endpoints and sample size generally not statistically driven. Patients recruited are generally ten or forty.

Feasibility studies are often required by FDA prior to pivotal study to assess basic safety and potential for effectiveness. Therefore, they are not intended to be the primary support for a marketing application. Pivotal studies, instead, have endpoints and sample size statistically driven. This typically requires a prospective, randomized, controlled, adequately powered clinical trial involving hundreds of patients. For that reason, they are generally intended as the primary clinical support for a marketing application. FDA review is much more complex [7].

2. Materials and Methods

Systematic review of scientific literature, analysis of websites of Competent Authorities, European Commission, Eurlex and FDA.

3. Results and Discussion

The comparison of the legislations on medical device studies between the USA and Europe has revealed that the basic concepts are similar. However, the way in which medical device studies are regulated in the EU is very different from the way they are regulated in the United States, especially in term of clinical data required for high risk devices. In the USA, the IDE procedure for high risk devices does not allow equivalence to be used for abbreviated requirements and the manufacturer is always required to perform one or more clinical studies, which can take one or more years. In Europe, also for high risk devices, equivalence can be used as part of the clinical evaluation procedures. This difference explains why certain devices can take several years longer to come onto the USA market, compared to Europe. As a result, the procedure for high risk devices is only used for 1% of the devices in the USA. This significant difference is illustrated by the example of the ORBERA™ Intragastric Balloon System. ORBERA™ is a non-pharmaceutical, non-surgical weight-loss system indicated in obese adult patients who have a Body Mass Index (BMI) of 30-40 kg/m² who have been unable to lose weight through diet and exercise. It consists of a soft, smooth silicone elastomer balloon that is placed in the stomach endoscopically and filled with a saline solution up to 650 cm³ through a self-sealing valve. The outpatient procedure takes less than 20 minutes, and the devices are removed six months later. Although ORBERA™ has been approved in many countries since the 1990’s, FDA approved the ORBERA™ system only in August 2015. The pivotal study of ORBERA™, which allowed FDA’s approval, was a multicenter, prospective, randomized, non-blinded comparative clinical trial. The study included 255 patients who were followed for one-year [8, 9]. Another example is provided by Elipse™ Gastric Balloon. In December 2015, Elipse™ has received European Marketing Approval. Elipse™ is not yet approved by the FDA and is not available for sale in the United States [10]. The curious thing is that manufacturers of both intragastric balloon systems are based in the USA.

4. Conclusions

The upon review explains why much early device testing takes place outside of the USA, and why the introduction of new devices into clinical practice is usually significantly delayed in the USA when compared with Europe. However, it cannot be stated that one system is better than the other one. In the European Union, device regulation should be more
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stringent without stifling innovation. In the USA, FDA should streamline the IDE procedure for high risk devices. However, after recent high-profile device failures, political pressure in both the United States and the European Union has favored more restrictive approval processes. In May 2016, the EU agreed new rules on medical devices and in vitro diagnostic medical devices with the aim of making sure innovative health care solutions and safety protection. The means of doing that are to strengthen the rules on placing devices on the market and tighten surveillance once they are available. For that reason, certain high risk devices, such as implants, may undergo an additional check by expert before they are placed on the market [11]. Changes in the FDA regulatory process have been suggested but are not imminent.

References


