

Bioequivalence Studies of Medical Devices - A Review of Constraints and Advantages



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Abstract

In most of the countries, the bioequivalence study and clinical trials for the medical device are not a mandatory prerequisite before launching of all classes of products into the market. At present the clinical study of medical devices is based on information from users. However, the advantage of conducting pre-launch clinical trials in cases of medical include benefits like the scope of improvement in design, potential safety threats, defining limitations of usages. In spite of several advantages of clinical trials and bioequivalence study, there is a sense of reluctance amongst the industry that hinders such studies. The protocols for each study shall widely varies due to differences and the technological features of each product. There is a need for an enhanced focus of scientists and academicians towards an appropriate study on clinical trials of the medical device in common interest of all stakeholders.

Keywords: Bioequivalence; Clinical trials; Medical devices; Babe; *In-vivo*; *In-vitro*

Abbreviations: BaBe: Bioavailability and Bioequivalence; CDSCO: Central Drugs Standards Control Organization; CT: Clinical Trials; USFDA: United States Food and Drugs Administration; WHO: World Health Organization

Introduction

The bioequivalence study has acquired much significance before registration of healthcare products with the drugs regulatory agencies across the world [1-5]. In case of generic pharmaceutical products, *in-vivo* study data is required in addition to that of for *in-vitro* study. However, the regulatory guidelines for conducting the clinical study or bioequivalence study for medical devices is very generalized and these documents lack specific directives to be followed by industry.

The clinical study and clinical trial refer to an overall philosophy of verifying the clinical advantages of using the healthcare products when subjected to the study volunteers. Bioavailability and bioequivalence (BaBe) studies provide logical confidence about the therapeutic use of any medicinal products. Bioavailability (Ba) refer the extent of drugs substance available for action into the body, whereas bioequivalence (Be) indicates the extent of drug substance available in pharmaceutically equivalent amount when tested into a living body. The typical practice diligently adhered in the clinical research organizations, is to conduct trials with at least clinical volunteers, who are older than 18 years of age. The clinical study design shall vary on the basis of device class and intended use.

Literature Review

There are a large number of studies available to describe the bioequivalence studies of generic pharmaceutical products because of its growing importance across the globe. as: However, the clinical study for medical devices are limited in numbers due to ambiguity of selection of reference products for comparison of clinical performance. The less number of study is due to feasibility constraints towards study. A few studies have described the best practices of clinical study of medical devices [6-10]. The critical aspects in such studies are the selection of study end point and correct volunteer's population [11,12].

Regulatory guidance for bioequivalence of medical devices and global practices

The bioequivalence studies have been declared the mandatory requirement for generic drugs to ensure the equivalence of quality, safety, and efficacy in several countries like Malaysia, but there is no emphasis on identical studies for medical devices [13]. Central drug standards control organization (CDSCO) in India has advised conducting the clinical study for disposable medical devices (e.g. syringe) wherever feasible. CDSCO has

made a mandatory provision bioequivalence study (BES) for conducting BES for inhalation products and the nasal sprays to compare the efficacy with respect to innovator's products [9]. World health organization (WHO) considers innovator's product as the most suitable reference for comparison [1].

World Health Organization (WHO) has categorically mentioned about the necessity of bioequivalence studies in case of essential medicines based on bio pharmaceuticals classification (BCS) and there is no mandatory guidance for medical devices [14]. The drugs and food administration of Ghana has developed guidelines for clinical trials for medical devices in addition to pharmaceutical products [15]. In fact, Ghana has issued a guideline on clinical trials with assistance from European agency EMEA [2]. The clinical trials (CT) have been described by International conference of harmonization.

The research gap and need of study

The clinical study is performed to compare the equivalence of pharmacological attributes of the devices under reference (e.g. innovator's device). The acceptance criteria for the clinical study is based on comparison results of pharmacological action. There are numerous varieties of medical devices available in global market. As per USFDA, there are about 1700 types of medical devices [16]. In view of their wide varieties and the limited number of research studies available, there is the requirement of the additional research study on medical devices.

Discussion

The bioequivalence study in case of medical devices may not be feasible in many cases such as, implant devices, cardiac pumps, selective organs etc. However, bioequivalence study has gained popularity in cases of metered dose inhalers, nasal spray etc. It is advisable that where ever, clinical trials are not feasible on living bodies, there should be adequate theoretical study under proper simulated conditions.

The clinical study centre should have sufficient facility and room to accommodate the volunteers along with their health verification room and bio analytical area. Following resources essentially required for the clinical study and of medical devices

Study protocols

A clearly documented protocol is the key to success of conclusive bioequivalence study programme. The study protocols may contain several aspects including pre validation of trails and designs of clinical study.

Volunteer class and their availability

The bioequivalence study is planned with an objective to treat a specific class of population. The racial, regional and topographical considerations are important criteria for selecting the population [12].

- a. The patient population that a study shall target

- b. The patient subgroup of population shall be included in the study
- c. Methodology for the study to be adopted
- d. Scientific views of stakeholders shall be concluded
- e. *Computer systems*

The data of bioequivalence study is quite voluminous and hence recommended to be handled electronically. There should be the adequate number of computer systems, qualified hardware, and statistical data processing software available in bioequivalence study centres. The above resources shall act as a tool for handling regulatory as well as business challenges against medical devices.

Results

The availability of volunteers for the clinical study is often a challenge for the research organizations. This task becomes even tough in for the clinical studies of critical medical devices, such as implants.

Constraints before the clinical study of medical devices

- a. The number of medical devices is the large and vitro study for all medical devices cannot be addressed by a common design due to different simulation requirement.
- b. The inherent technological knowhow of sophisticated medical device that hinders the clinical studies.
- c. The data of plasma concentration is made the basis of drugs impact evaluation, which is an unlikely criterion in all cases of the clinical study of medical devices.

Advantages of the clinical trials and bioequivalence

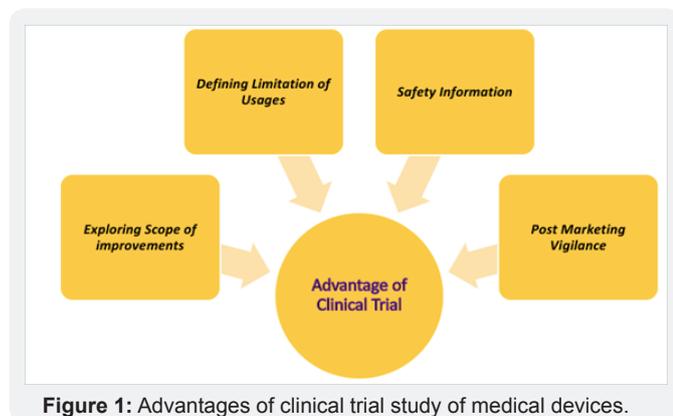
The clinical studies of medical devices may open several opportunity in interest of customers as well as industrial enterprises. The clinical study and bioequivalence study data have several benefits and out of them a few areas under,

Exploring scope of improvements: The study provides a pathway to the improvement in the design of medical devices. The clinical study of medical devices also brings about the idea for launching similar new products with the competitive technological edge.

Defining limitation of usages: Based on study data and their conclusion, the prospective users can be prescribed instructions and limitation of device usages. The information about limitation becomes important in cases of over the counter medical devices, which are used without assistance from health practitioners.

Safety information: The comprehensive information about the precautions shall help the device manufacturer to mention the safety information to further prevent the adverse impact reporting and complaints from customers.

Post marketing vigilance: Clinical trials help a device manufacturer to identify the need for post-marketing vigilance against the distributed products [8]. As per conclusion of a clinical study, the device may have to issue helpline and customer support number for advising the users during an emergency (Figure 1).



Conclusion

The study shows that there are limited number of guidelines available for medical device manufacturers to give direction towards clinical trials and bioequivalence study. There are numerous challenges in conducting the clinical trial and study before launching of the medical device, however, this has substantial advantages to finally augment patient's confidence on products. There is need of more study related to clinical trials of medical device either *in vivo* or *in vitro* studies. Researchers are recommended to establish the financial and ethical benefits of conducting clinical trials, bioequivalence and bioavailability study before launching of new medical devices Following resources essentially required for the clinical study of medical devices.

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