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Why preclinical testing of medical devices is important to health care communities?

King Solomon Ebenezer *, Rekha Manivanan, Chidambaram Tamilselvan, Keerthana Namachivayam and Nishanthi Thirugnasambandham

Department of Drug Discovery and Microbiology, Bioscience Research Foundation, Chennai, India.

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Abstract

Medical devices is a crucial to modern medicine because they aid in the diagnosis, treatment, and monitoring of a wide range of medical conditions. The effectiveness, biocompatibility, and risks of the devices need to be validated in animals before they could be successfully and safely implemented in clinical practice. In this preclinical evaluation stage, animal models continue to act as an essential bridge between in vitro experiments and human clinical trials. The basic biocompatibility tests and the significance of using animals in medical device testing are discussed in this communication.

Keywords: Biocompatibility; Rat; Mice; Guinea Pig; Rabbit; ISO; USFDA

1. Introduction

Globally, the important considerations of animal model development and testing of medical devices is to reduce risks on the human. So while testing the medical device it will not tested as such, there are some regulations and guidelines in place to ensure that animals treated humanely and to minimize the use of animal in the research whenever testing.

Ethics must be considered while using animals in medical device testing need to be thoroughly considered by scientists and government organizations to make well-informed decisions to strike the requirements of science with ethics and compassionate care of animals. FDA recommended the animals to evaluate the medical device for the human use (FDA, 2023).

The use of animal models in medical device testing is an essential phase in the development process. Even while breakthroughs in alternative testing methods are being investigated, animal models remain a vital resource for obtaining extensive knowledge into the safety and efficacy of medical devices, which ultimately helps to improve patient outcomes in clinical practice.

Post-market monitoring is a crucial component of many regulatory frameworks, as it allows us to track the efficacy and safety of medical devices after they are placed on the market. It is often mandatory for manufacturers to report adverse events and address issues as soon as they arise. So, the testing of medical devices to be mandatory before marketed.

2. Major Regulations for Medical Devices

The FDA regulates medical device regulation in the US under the Federal Food, Drug, and Cosmetic Act (USFDA). The regulatory process for devices may encompass the De Novo pathway, premarket approval (PMA), or premarket notice (510(k)), reliant on the risk classification of the device. The USFDA needs the tests to be performed under the 21 CFR

* Corresponding author: King Solomon Ebenezer

part 58 (Good Laboratory Practices). The Quality System Regulation (QSR) specifies Good Manufacturing Practices (GMP) to produce medical equipment.

The EU introduced the Medical Device Regulation (2017/745), which amends the Medical Device Directive (93/42/EEC). MDR imposes higher standards for product safety and clinical evidence. It has a Unique Device Identification (UDI) system in addition to a more extensive post-market surveillance mechanism.

Under the Medical Devices Regulations, Health Canada oversees the regulation of medical devices in Canada. The regulatory process, which is like that in the US, includes compliance testing and the classification of Class I to IV devices. Devices in classes III and IV required premarket approval.

Medical equipment is regulated under the Pharmaceutical Affairs Law of Japan, which is enforced by the Pharmaceutical and Medical Device Agency (PMDA). Premarket approval and post-market surveillance are managed by the PMDA, which ensures the safety and efficacy of medical devices marketed in Japan.

The TGA oversees overseeing medical devices in Australia. The regulatory process includes conformity evaluation procedures based on device classification. The Australian Register of Therapeutic Goods maintains an up-to-date list of approved devices (ARTG).

Organizations like the International Organization for Standardization (ISO) provide international standards for medical goods. Compliance with international standards were such as ISO 10993 for testing and ISO 13485 (Quality Management Systems for Medical Devices) for manufacturers.

3. Major Preclinical Practices

Preclinical researches on animals need to be periodically conduct on medical devices to evaluate their safety and effectiveness prior to human testing. This helps identify potential benefits and risks. Animals have been used in medical device testing and development processes in a variety of ways. These are a few common uses of animals in medical device research. When determining if medical devices biocompatible involves evaluating the device's compatibility with living tissues and the immune system etc. Animals can be used in research on the susceptibility of medical equipment to infection and the effectiveness of antimicrobial coatings or treatments. Translation of novel products form preclinical to clinical is complex (Lottes *et al.,* 2022)

Medical device testing is influenced by the kind of device, its intended use, and applicable regulations. When selecting which animals to test medical devices.

Implant device: Implant testing in animals need to be evaluate the long-term effects of devices, like pacemakers or prosthetic joints, on surrounding tissues and overall device performance.

Cardiovascular Devices: Cardiovascular Device Testing: Animals, particularly pigs and dogs, are commonly used in the testing of heart valves, stents, and other cardiovascular devices.

Wound Healing products: Research on the potential of medical devices to heal wounds has been conducted on rats and other animals. This is essential for products like dressings, sutures, and other substances intended to hasten the healing process.

Significance for Human Physiology: Choose animal models that resemble humans in terms of anatomy and physiology, especially in the target organ or system that the medical device will be treating. This similarity helps predict how people would use the device.

4. Consideration of Animal Models for Testing

Consider if the medical issue or application for which the device is designed have any established and well-defined animal models available. Rats, mice, rabbits, dogs, pigs, non-human primates, and pigs tend to be utilized as animals.

Ethics and Laws: Adhere to all applicable laws and rules regarding the use of animals in research. Regulations governing organizations may impose limitations on the selection of animal models to guarantee humane treatment and ethical considerations.

Consider the animal's physical characteristics and proportions in connection to the medical gadget. Larger animals might be more appropriate for testing apparatus meant for usage in larger human patients, whereas smaller animals are probably more suited for testing applications or smaller equipment.

If the medical equipment is intended to be used for an extended period, select animal models whose lifespan allows the assessment of chronic impacts.

Certain technologies, particularly implants, may require long-term research to assess their potential effects and lifespan.

Use animal models of diseases that either naturally occur or may be induced to develop to test medical devices designed to treat specific diseases or conditions. When it comes to testing equipment for neurological, diabetic, and cardiovascular disorders, this is particularly crucial.

5. Rationale for Animal Models

By utilizing animal models, which are selected for their physiological similarity to humans, researchers can gain insight into the potential interactions that a medical device may have with biological tissues and organs. When evaluating implantable devices, such as stents, prosthetic joints, or heart devices, this similarity is particularly significant.

The complex biological reactions, such as immune responses, tissue repair, and potential adverse consequences, that living organisms have to medical devices cannot be entirely replicated in vitro. Animal models offer a more thorough understanding of these processes in a living system.

In many cases, extended monitoring periods are required to assess the safety and long-term impact of medical equipment. Using animal models, researchers may monitor the long-term effects, issues, and general endurance of devices before moving on to human trials.

The choice of animal species and strain is critical and depends on the special characteristics of the medical device as well as its intended use. Among the often-used animals are rats, mice, rabbits, dogs, pigs, and non-human primates; each was selected according to how pertinent it was to the intended medical condition.

Using animal models raises important ethical concerns. Researchers must adhere to strict regulatory requirements and ethical guidelines to ensure humane treatment and minimize the use of animals whenever possible.

Applying results from animal models to human physiology is a crucial consideration. The selected animal models scientifically verified data able to adequately forecast how the medical gadget will function and interact with the human body.

6. Biocompatibility Tests

Studies on biocompatibility are crucial for evaluating how medical devices and materials interact with biological tissues. The International Organization for Standardization (ISO) produced the ISO 10993 family of standards, which serve as a framework for these assessments. Guidelines for medical device biological evaluation can be found in the ISO 10993 series. The following are some of the biocompatibility study types that are specified in ISO 10993 guidelines (Table 1).

Table 1 List of Biocompatibility tests with standards

Tests	Test system	Standards	Concepts	References
Biological Evaluation Plan	-	ISO 10993-1	Recommends creating a Biological Evaluation Plan (BEP) before conducting biocompatibility testing. The BEP outlines the general methodology for assessing the biological safety of the medical device	Biological evaluation of medical devices — Part 1: Evaluation and testing within a risk management process. ISO 10993:1, 2018

Cytotoxicity	L929 Cells	ISO 10993-5	This study evaluates a material's or device's ability to cause damage or kill cells.	Biological evaluation of medical devices — Part 5: Tests for in vitro cytotoxicity.
Sensitization	Guinea Pig	ISO 10993-10	Sensitization tests assess a material's or device's capacity to cause an allergic reaction.	Biological evaluation of medical devices — Part 10: Tests for irritation and skin sensitization.
Irritation and Intracutaneous Reactivity	Rabbit	ISO 10993-10	Assess whether an item or device has the potential to cause skin irritation or inflammation when it comes into contact with them.	Biological evaluation of medical devices — Part 23: Tests for Irritation.
Systemic Toxicity	Mice	ISO 10993-11	Assess the material or device's potential negative consequences before allowing it to enter the bloodstream. This covers evaluations of acute and sub-chronic toxicity.	Biological evaluation of medical devices — Part 11: Tests for systemic toxicity.
Pyrogenicity	Rabbit	USP 151	Reduce the patient's risk of experiencing a febrile reaction after receiving the relevant product via injection to an acceptable level. The test is intended for product that the test rabbit may tolerate at a dose not to exceed 10 mL/kg provided intravenously within a period of NMT 10 min. It measures the rise in temperature of the rabbits after they receive an intravenous injection of a test solution.	United states of Pharmacopeia.
Implantation	Rabbit/Rat	ISO 10993-6	Involve evaluating the biological reaction that a material or devices will have when it is inserted into living tissues. The research might examine at both acute and long-term implantation modes.	Biological evaluation of medical devices — Part 6: Tests for local effects after implantation.
Subacute and Sub-chronic Toxicity	Rat/Mice	ISO 10993-11	Assess the consequences of extended contact with an item or equipment. Animal models may be given materials or extracts as part of sub-acute and sub-chronic studies.	Biological evaluation of medical devices — Part 11: Tests for systemic toxicity.
Chronic Toxicity	Rat/Mice	ISO 10993-11	The effects of long-term exposure to a material or device. They may include extended exposure periods and continuous monitoring of biological responses.	Biological evaluation of medical devices — Part 11: Tests for systemic toxicity.

7. Importance of Rigorous Testing Medical Devices

- The primary focus when creating medical devices to be patient safety. By testing products before they come on the market, medical device manufacturers can assist in identifying potential risks and unfavorable outcomes associated with the use of such devices.
- Testing is necessary to assess the functionality and efficacy of medical devices. It helps verify whether a device operates as intended, produces accurate results, and provides the expected therapeutic advantages. Reliable performance is necessary for the ideal feasible patient outcomes.
- Strict specifications remain enforced for approving and advertising medical devices from the US Food and Drug Administration (FDA), the European Medicines Agency (EMA) in the EU, and other regulatory authorities throughout the world.
- Testing ensures compliance with these regulations, facilitating commercialization and legal distribution.

- Medical device testing must be performed for complying with strict manufacturing quality standards. Following Good Manufacturing Practices (GMP) reduces the possibility of errors and malfunctions by ensuring that products are consistently manufactured in accordance with quality standards.
- Medical device imperfections or weaknesses can be discovered through testing. Manufacturers can enhance the devices' overall functionality and design by implementing the required modifications according to data provided from testing.
- Testing for biocompatibility evaluates how a technology works on the living tissues, and to guarantee that the component of the device does not produce any adverse effects when contact with human body.
- One of the most important parts of the medical device risk management process is testing. It helps manufacturers identify and assess possible hazards associated with the use of their devices and implement systems in place to mitigate such risks to ensure a positive risk-benefit profile.
- To identify any new risks or unanticipated issues, post-market medical device monitoring requires that continue. Testing supports post-market surveillance, enabling timely resolution of safety concerns and the evolution of technology.
- Medical technology safety and efficacy possess a direct impact on global public health. Ensuring that medical devices pass rigorous testing requirements helps to maintain public and healthcare professional confidence in the safety and efficacy of these advances in medicine.

8. Conclusion

Ensure patient safety, regulatory compliance, and the efficacy of medical therapies, biocompatibility testing of medical devices is necessary. With comprehensive assessments of the materials' interactions with biological systems, these studies offer crucial information on potential hazards like toxicity, inflammation, and immunological responses. At ultimately, thorough biocompatibility testing promotes patient confidence and safety in the reliability and quality of medical devices, promoting innovation in healthcare while focusing a high priority on safety. Testing for regulatory biocompatibility is critical for assuring the efficacy, safety, and quality of medical devices. It emphasizes the dedication to patient care while promoting technological developments in medicine that help patients and healthcare professionals.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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