
reference paper

Charles River Laboratories

Volume 10 #2 1997

Animal Models in Medical Device Development and Qualification

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Introduction

The biological evaluation of medical devices and device materials is an extremely complex task. The team charged with the oversight and conduct of such studies usually includes representatives from the disciplines of medicine, veterinary medicine, biology, pathology, engineering, and materials science. Also involved should be representatives from the functional areas of regulatory and clinical affairs, quality assurance, manufacturing and marketing.

No single study will answer all the questions that need to be addressed in the development of medical devices. Each device design is unique and requires a customized series of studies to provide data on the biocompatibility and toxicity of all materials. Depending on the clinical application, the safety of the device prior to its use in a human must also be proven.

This paper will discuss the general process and principles to be considered when selecting animal models for medical device development and qualification.

Where possible, specific examples and discussions have been drawn from the cardiovascular device industry.

Medical Device - Definition and Classification

A medical device, as defined by the International Organization for Standardization (ISO), is "any instrument, apparatus, appliance, material or other article, including software, whether used alone or in combination, intended by the manufacturer to be used for human beings solely or principally for the purpose of:

- diagnosis, prevention, monitoring, treatment or alleviation of disease, injury or handicap
- investigation, replacement or modification of the anatomy or of a physiological process
- control of conception

and which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means."¹

The nature and duration of contact with the body are the basis of medical device classification, and each will

influence the extent of necessary biocompatibility and safety testing.²

Based on the nature of their contact with the body, devices are classified as either surface- contacting, external communicating, or implantable. Surface-contacting devices may directly come into contact with either the skin, mucous membranes, or a breached or compromised surface. Examples of devices included in this category are: electrodes, skin tape, contact lenses, orthodontic appliances, stomach tubes, and occlusive patches.

External communicating devices are those which either indirectly contact the blood path, communicate directly with tissue, bone or dentin, or directly contact circulating blood. Examples include: intravenous administration sets, dental cement, skin staples, blood oxygenators (Figure 1), and balloon catheters (Figure 2).

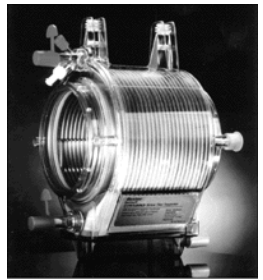


Figure 1.

Implantable devices are those which are implanted into the body and thus directly contact either tissue, bone, or blood. Ventricular assist devices, heart valves, vascular grafts (Figure 3), artificial joints, bone screws, and breast implants are typical devices included in this category.

The duration of contact may be limited, prolonged, or permanent. Limited contact devices are those where the exposure period occurs for up to 24 hours. Prolonged exposure devices are those where the exposure or use is greater than 24 hours but less than 30 days. Devices in which use or contact is likely to exceed 30 days are considered to be permanent. Thus, a permanently implanted device would require the most rigorous testing plan.

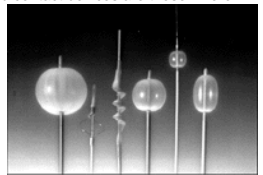


Figure 2.

Guidance

There are a number of sources which may provide guidance in designing test plans for prototypical medical devices. Most guidance documents are relatively nonspecific in nature and require the application of sound scientific method to the specific device in question. However, some guidance documents may be relatively specific and may suggest which tests or animal models should be used.

The selection of testing regimen for the evaluation of biological responses of devices and/or materials is outlined in the ISO 10993-1 standard^{1,2}. This document serves as a guide- line for meeting the essential safety require- ments of the European Union's Medical Devices Directive and CE Mark certification. The Food and Drug Administration (FDA), which must approve or clear all medical devices for use in the United States, likewise provides guidance for many, though not all, types of medical devices. The battery of biocompatibility tests required by the FDA is determined by a matrix contained in the FDA's General Program Memorandum -- #G95-1.³ Though there are a few exceptions, the testing required by the FDA closely parallels that of ISO 10993-1. The FDA also provides some guidance on safety and effectiveness testing for certain types of devices.

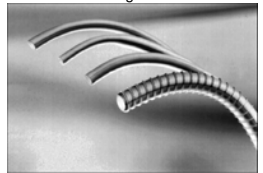


Figure 3.

Guidelines from the FDA and ISO are not necessarily the only guidance documents available. Many countries have developed their own requirements which may or may not harmonize with ISO or FDA requirements. The reader is encouraged to seek regulatory advice in developing a preclinical testing plan to ensure maximum utilization of the testing results in support of worldwide marketing applications.

In addition to the above regulatory guidance, testing guidance suggestions from organizations such as the Association for the Advancement of Medical Instrumentation (AAMI), the American National Standards Institute (ANSI), or from the proceedings of professional meetings or convened committees are sometimes available. This may depend upon the device and application.

Finally, the literature may provide some guidance in the form of models which have been used in past studies. In situations where there is little or no official guidance, the testing and model choices must be determined by the manufacturer and will have to be justified to the regulatory bodies.

Preclinical Testing

Preclinical testing encompasses testing of all materials and prototypical devices prior to testing or use in humans. This testing is generally conducted in order to provide a reasonable assurance of device safety prior to use in humans in a clinical trial. It should be noted that, in the case of some devices, the animal testing and

in vitro data alone may satisfy regulatory requirements for device approval and sale. Model selection in these situations be- comes all the more critical. Preclinical testing includes both in vitro and in vivo biocompatibility/toxicity testing, in vitro device testing, ex vivo device testing, in vivo feasibility testing, and in vivo testing for safety. Biocompatibility testing may be performed on whole devices or individual material components which make up a device.

In vitro device testing includes all non- animal testing and often evaluates specific immunological, chemical, or physical properties of devices. Tests such as creep resistance of vascular grafts, burst pressures of catheter balloons, and accelerated life testing of heart valves are examples of common in vitro tests.

Ex vivo device testing is performed most often on external communicating devices which involve circulating blood, such as hemodialysis units and oxygenators.

In vivo feasibility testing may be performed in a variety of animal species to define or refine a model. This is important in gathering preliminary information on the safety and, in some cases, effectiveness of a device. In vivo safety testing for regulatory submissions should be conducted in accordance with Good Laboratory Practices (GLP).⁴

In the testing which occurs during the development of a medical device, animal model selection is influenced by three sets of characteristic parameters. These are the characteristics of the biomaterial components, the characteristics of the device design, and the characteristics of the animal. Each set of characteristics must be considered in the process of determining which tests and which models should be employed. In all cases, the device and materials being evaluated should be representative of the processes anticipated in the manufacturing and sterilization of the final product.

Characteristics of Biomaterial Components Which Influence Animal Model Selection for Biocompatibility Testing

Biocompatibility testing takes into account the nature and duration of exposure to each component, the chemical and physical nature of each component, the biological activity of any additive or residue chemicals, leachable substances, metabolites or biodegradation products, the biological interactions between components, and the effects of sterilization. The battery of tests and specific animal models are selected based on the nature and duration of contact. Less rigorous testing would be required for surface contacting components as opposed to permanent blood contacting implantable components.

It may be possible to waive some portions of the biocompatibility testing based on a material's long history of use in currently marketed devices and evidence in the literature to support acceptability for the test in question. It is the responsibility of the manufacturer to provide evidence to support petitions for waiver.

A comprehensive battery of biocompatibility testing will usually include tests for cytotoxicity, sensitization, irritation, intracutaneous reactivity, acute systemic toxicity (<24 hr), subacute toxicity (>24 hr and <10% of total life span of the model species), genotoxicity, implantation, hemocompatibility, chronic toxicity (>10% of the life span of the model species), carcinogenicity, reproductive and develop- mental toxicity, and biodegradation. Examples of specific animal models used for biocompatibility testing are:

- guinea pig maximization test (sensitization test)
- USP rabbit irritation and intracutaneous reactivity
- mouse systemic injection (acute toxicity)
- rabbit intramuscular implantation test
- USP rabbit pyrogenicity test

Each animal model should be assessed for its ability to predict what is likely to occur in the human. Due to unique sensitivities or other complicating circumstances, certain animal models may not be applicable for certain biomaterials.

Many in vivo biocompatibility tests have been supplemented or, in some situations, re- placed by in vitro alternatives. Procedures such as the Agar Overlay Test and Medium Eluate Method (MEM) for cytotoxicity, the Ames mutagenicity test for genotoxicity, the Limulus amoebocyte lysate (LAL) for pyrogenicity, and the kallikrein contact activation assay for hemocompatibility are examples of in vitro tests which may have application in the specific biocompatibility testing plan for a new medical device.

Limitations

There are limitations to all biocompatibility and in vitro testing procedures. Most of these tests examine very specific parameters each of which may or may not be representative of the actual application of the

functioning device. The tests are generally conducted outside the complex and dynamic physiological environment in which most medical devices are placed. It may not be possible to accurately assess the interactions between the various systems of the body, combined with the physical demands of a functioning device. In addition, implanted biomaterials, when implanted for prolonged periods, may undergo changes in compliance, chemical content, and other important properties which may lead to failure or other untoward event.

Characteristics of Device Design Which Influence Animal Model Selection

There are many characteristics of the design of a medical device (failure modes, the duration of the evaluation period, the size of the device, the application/intended use, and the regulatory strategy to be employed) which may have an influence on the selection of the animal model for in vivo feasibility and safety studies.

Failure Modes

Some of the most important characteristics of a medical device which affect animal model selection are the potential failure modes of the device. Failure modes are the likely problems which might be seen in a clinical situation and which need to be minimized prior to use in humans. As a rule, failure modes are very specific to the design and components of each device. Minor component changes (such as changing the cloth in the sewing ring of a bioprosthetic heart valve) can affect the significance of a specific failure mode (such as excessive tissue overgrowth). This may result in a more rapid or increased rate of failure. Likewise, minor design changes, when coupled with exposure to manufacturing and sterilization processes, may lead to an unexpected increase in component stress and an increased incidence of fractures.

For devices implanted into the cardiovascular system, the most common failure modes include: thrombosis, embolism, excessive tissue proliferation, hemolysis, bioprosthetic tissue failure (degeneration, calcification, tearing) and mechanical failure (wear, fracture, dilatation, etc.). Each specific device will have its own inherent failure modes. For mechanical heart valves (Figure 4), these would include thrombosis, hemolysis, and mechanical failure. For bioprosthetic heart valves (Figure 5), these would more likely be excessive tissue proliferation and bioprosthetic tissue failure (usually calcification). Proper animal model selection thus depends on a given model's potential to reproduce a specific failure mode.

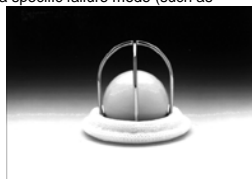


Figure 4.

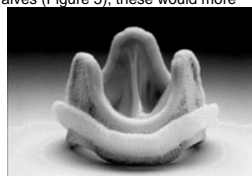


Figure 5.

Duration of Contact

Animal model selection is also influenced by the intended duration of contact or the useful life span of the device. As previously described, this duration is a determinant of the types of studies which must be completed.

Relatively short term external communicating devices, such as hemodialysis units whose utility is a period of hours, should be tested under conditions of actual use, especially with respect to duration of test procedure, blood pressures and flows, and anticoagulation regimen.

With prosthetic heart valves it is generally impractical and cost prohibitive to test for the useful life span of the device in vivo which, in the case of mechanical heart valves, may be decades. In such a situation, the manufacturer must select study time points based upon the device's likely failure modes and an animal model's ability to reproduce that failure mode within the time constraints selected. This can be difficult since failure may occur from complications related to the animal rather than the failure mode being tested (e.g., outgrowth of a valve, infection, or excessive tissue response). The presence of these confounding variables often necessitates a larger number of animals be placed on test to gain reasonable assurance that the results are reliable.

Size and Application of the Device

The size of the device and the site of the intended clinical application obviously have a dramatic influence on the animal model to be used. A key point to consider is whether the device (or section of a device) fits within size constraints of the animal model, preferably at the site of intended use, and with minimal disruption of homeostasis. This impacts the testing plan from several perspectives and, for many devices, this characteristic eliminates many animal models from consideration.

In situations where a device would be too large for a specific model species, the question of whether a

smaller iteration could be produced, at what cost (labor, time and equipment), and whether it would be representative of the human clinical-sized device then becomes important. Due to the complexity of the manufacturing process many types of medical devices are extremely difficult to miniaturize. In addition, the downsized device, when used in the smaller animal model, may exhibit significantly different clinical characteristics and failure modes than the clinically sized device, which is designed to be used in a human. This may be due to differing site dynamics, rheology, pressures, or other model characteristics. For this reason, most safety testing involving mechanically functioning devices is conducted in relatively large animals, such as rabbits, dogs, pigs, goats, sheep, cattle and large primates.

Regulatory Strategy

The regulatory strategy to be utilized when seeking marketing approval may also influence testing and animal model selection. All labeling claims must be detailed within regulatory submissions and claims should be supported with human and/or animal data. Studies should thus be designed to support a human clinical trial (if required) and the labeling claims. With respect to approval by the FDA, a manufacturer must request either a "510(k)" (market clearance) or seek PreMarket Approval (PMA) depending on the risk classification of the device. In a 510(k) submission (referring to section 510(k) of the Federal Food, Drug, and Cosmetic Act)⁵, the applicant must provide evidence that the new device (1) is substantially equivalent to a currently marketed device, (2) does not sustain life and (3) would not result in a life threatening situation upon failure.

In designing a study to support a 510(k) application, it is generally preferable to utilize similar models to those which were used to support market clearance of the initial device and to which equivalency is being claimed. This often reduces the number and types of studies which must be conducted. An additional advantage of using this strategy is gained by using the currently marketed device as a control for the studies. This practice greatly simplifies the complexity of the experimental design and may facilitate the approval process.

A PMA application is necessary for new significant risk devices, including permanent implantables, and those devices which sustain life or in which failure would result in an unreasonable risk of injury or illness. These types of devices generally require a large battery of very thorough testing to demonstrate safety. Often in such cases, new animal models must be developed and validated through feasibility studies prior to the conduct of the safety studies.

Characteristics of the Animal Which Influence Animal Model Selection

Anatomy

The structure of a specific organ or system, including the microscopic anatomy, may affect model selection by virtue of similarity or lack thereof to man. The presence or absence of specific structures may be integral to the success or function of a specific device. Alternatively, the presence of a specific structure may prevent the proper functioning of a specific device. As an example, the microscopic anatomy and the blood supply to the conduction system of the heart of the pig is much more similar than other animals to that of man.

In addition, the distribution of the pig's coronary arterial circulation and the collateralization of the blood supply following infarction is very similar to man but unlike that of other species such as the dog.⁶ However, unlike man, the pig has a left azygous vein returning blood directly to the heart via the coronary sinus.⁷ Thus when selecting models for evaluation of coronary arterial grafts, implantable pacemakers, or bypass applications, these characteristics may be significant.

In addition to structural anatomy, the size of and accessibility to the structure must be compatible with clinical device function and use in man. For testing certain types of percutaneous vascular devices, the size of the access artery (femoral artery) must be similar to that in man (approximately 8-10 mm in diameter). Few common laboratory animals have a femoral artery this large. The young bovine does have an artery of appropriate diameter; however, the bovine vessel is typically located considerably deeper than in the human. This depth may affect the successful use or function of the device.

A final anatomic characteristic which must be considered in planning device testing studies is animal growth. Often the most appropriate animal for testing a specific device is a relatively young porcine, ovine, or bovine. However, due to rapid growth rates in these species, unnatural device failure modes may be created when these animals are entered into longer term studies (>4 months). This may be seen with cardiac and vascular devices where valves or grafts are sized specifically for the individual at the time of implantation. Growth of the vessel or heart results in a functional stenosis several months into the study as the animal outgrows the device.

Occasionally testing of pediatric cardiovascular implantable devices requires a growth component. In this case the porcine growing heart model may be utilized because it simulates, in approximately six months, the

size increase which occurs in human hearts from birth to maturity.⁸ This model has been used to test a number of devices including flap angioplasty, prosthetic atria, and grafts for correcting congenital defects.⁹ In situations where the pig is the most appropriate model species except for an unacceptable growth rate, the smaller, slower growing minipig or micropig may be utilized. These animals have mature adult weights comparable to humans and may be preferable for long-term studies.

Physiology

With respect to physiology we are again faced with similarities to and differences from the human clinical situation. Similar physiologic parameters such as regional blood flow, cardiac output, end diastolic volume, or blood pressure may be necessary in the animal model to test or validate the performance of a device. Likewise, significant differences between human and model physiologic parameters may invalidate a proposed model. Manipulation of physiologic parameters is also a desirable characteristic of an animal model. For example, the evaluation of a new algorithm for a cardiac output monitor must be validated not only at standard heart rates and cardiac outputs but at the extremes of the possible human ranges. Thus a model whose parameters can be manipulated must be utilized to test this type of device.

Species specific metabolism may play a significant role with respect to biologically active devices such as pancreatic islet transplant devices. Implants into species in which the metabolic processes differ greatly from that of man may result in a false failure mode. Host metabolism may also play a role, as previously discussed, with respect to failure of devices due to metabolic breakdown of device components.

Reactivity means that the tissue, organ, or implant site responds similarly in the model as it would in man. Examples of situations where animal species reactivity may influence model selection would include: intimal proliferation within vascular grafts or conduits, thrombus formation on mechanical valve leaflets, fibrosis around a biological device (prohibiting its function), and wound healing over prosthetic skin grafts.

Diseased Models

The use of a diseased animal model may be recommended, especially for device effectiveness testing. In this situation, the decision process should involve discussion of both induced and natural models. There are many natural animal models of human diseases and most have been well characterized. Unfortunately, these animals may be limited in availability, are usually expensive, and may exhibit variable "severity of disease". Induction of specific diseases or conditions in animals has also been accomplished for most human diseases. This may involve drug treatments, surgery (or surgeries), specialized diets, or other activities followed by a waiting period for the condition to develop.

When considering the use of a disease model, one must be aware of the extent to which the model simulates the human condition and the specific actions of the device being tested. Induced and natural animal models may exhibit certain pathologic changes that are very different from those seen in the disease in man. For example, there are over twenty different natural and induced models of atherosclerosis. Unfortunately few of these models develop plaques which simulate human atherosclerotic plaques in morphology, composition, and/or location. This is why, in its guidance for interventional cardiology devices, the FDA recommends specific induced atherosclerotic models.¹⁰ The lesions in the recommended models are repeatable, very similar (though not identical) to atherosclerotic plaques in man, and useful for demonstrating safety and effectiveness of various interventional cardiology devices.

Non-diseased Models

Non-diseased animal models have advantages in that they are generally readily available, are relatively less expensive, and may be used in a more timely manner. These models also permit an experimental design without the inherent complications (anesthetic risk, animal death, etc.) associated with many disease states. Unfortunately, non-diseased animal models may have different reactions than their diseased counterparts. This may be important when assessing implantable devices since a normal animal may react somewhat differently than does the diseased animal or a diseased human. Depending on the device, non-diseased animal models may be used to demonstrate both safety and effectiveness or alternatively, may be used solely to demonstrate safety. Effectiveness assessment would then be demonstrated in human clinical trials.

Genetics

The genetics of the model plays an important role in selection of specific natural disease models as well as in biocompatibility testing. Most natural disease models have a genetic predisposition to the disease condition in question. For biocompatibility testing, inbred strains of rodents (if they are sensitive to the material) usually provide a more consistent response than outbred stocks. The outbred stocks, however, may be more reflective of the true risk to the human population which is genetically diverse.

Husbandry

Animal husbandry can affect the model selection in a number of ways. From a facility management perspective, the housing, equipment, and expertise appropriate to the species and the study must be available. This may include veterinary or veterinary technical care, medical and anesthetic equipment, pens, cages, runs, exercise yards, tethering devices, etc. Some types of housing may be incompatible with the function of some devices. The cost of the animal may likewise influence its use in this time of shrinking research budgets and increasing research costs.

The source/supplier of the animal should be reputable and their operations should conform to accepted practices, guidelines and regulations. Many manufacturers also require auditing of animal supplier facilities, a process which will determine if facilities and practices are in place that will assure a continuing supply of uniform, healthy animals. Transportation methods and conditions, as well as availability throughout the testing program, are also important considerations. For many of the genetically diseased models, availability can be a significant challenge, since there are usually limited numbers.

The health status of the animals is also very important. Long conditioning periods are costly and can delay a project. Unhealthy animals inadvertently placed on study often result in non-experimental variability including false positive toxicity tests, device failures, infections or other reactions which must be further investigated or may invalidate a study. The animal supplier should have in place appropriate quality control and assurance programs to insure that the health and genetic status of the animals being provided are in accordance with testing requirements.

Species typical behavior may play a role in model selection. Some species may cannibalize surgical wounds, pick out sutures, or be difficult to handle, treat, or sample postoperatively. Frequent handling of some species may create non-experimental variability by causing stress and affecting physiologic, hematologic, and clinical chemistry parameters.

Device Placement and Post Procedural Complications

An important issue that relies heavily on animal model selection is whether the surgical team can successfully reproduce the device placement procedure in the selected model species. Many surgical procedures which are routinely performed in humans can be more difficult to perform in some species of animals even by very skilled individuals. Swine, for example, are known to have cardiac and vascular tissues which are very fragile, hence delicate surgical technique is extremely critical. Depending on the degree of technical difficulty, a manufacturer may prefer an experienced surgeon placing the device; a practice which should reduce or eliminate device failures related to surgical technique rather than device performance.

Complications can also arise because there are differences among animal species in responses to procedures such as cardioplegia, long periods of anesthesia, or cardiopulmonary bypass, as well as in behavior following major operative procedures. Infections also pose a complication risk since some species may harbor opportunistic pathogens which cause primary infections of prosthetic devices during the experimental period. Increased susceptibility to such complications may prevent the successful use of an otherwise ideal animal model.

Summary

Disdisheim et al summarized the goal of the preclinical animal testing process when they suggested that biomaterials or prosthetic devices should be evaluated preclinically under conditions which simulate their intended use as closely as possible with respect to duration of exposure (within reason), pressure, flow, rheologic conditions, and geometry of the device. The testing should evaluate a particular problem (thrombosis, pseudointimal proliferation, calcification, or mechanical failure) using the appropriate species and age of animal for the appropriate duration in the development of the particular problem.¹¹ This requirement, along with the factors covered in the preceding text, reinforces the notion that selection of an animal model for preclinical medical device testing is a complex and often difficult task. Rarely can all of the previously stated conditions be met. So how do we approach this task?

First of all, these principles for animal model selection apply to all devices. As part of the study design process prior to preclinical testing, a risk assessment of both the component materials and the completely assembled functioning device should be conducted to define the most likely failure modes.¹² The resulting failure modes should be ranked as to likelihood of occurrence, and potential animal models should be selected based on their ability to predict the failure modes in question.

During feasibility studies, each potential model should be evaluated based on the biomaterial, device, and animal characteristics as to whether it may be appropriate for safety studies. At this point there may be some compromises between ideal model characteristics and which models are available and have a probability of successful device placement. Models in multiple species may be necessary in order to define different failure

modes.

After a model is selected, a very specific and detailed protocol should be written to define the exact conduct of the study. The study should be designed to provide data on safety and, if possible, effectiveness, support applicable label claims, and provide for the requirements of applicable guidance documents and/or regulatory bodies.

For some devices model selection may be relatively simple, since selection based on device characteristics or model similarities to man would not necessarily yield more clinically meaningful data. In such a situation, selection should be based on more logistical considerations such as surgical and anesthetic team experience, availability, ease of handling, cost, etc.

Proper animal model development for medical device testing is costly both in time and money. Project milestones and budgets should adequately reflect these factors. These costs can usually be reduced by including the laboratory animal veterinarian or other animal research specialist on the team very early in the development process. This allows for planning within the animal facility, model research and development, detailed protocol writing, animal or equipment acquisition, training and documentation, and the myriad of other activities involved in managing animal studies. The time and money invested in well designed medical device testing, based on sound scientific principles and proper animal model selection, should more than offset the loss of time, money, and market exposure which occurs when the introduction of a medical device is delayed due to poorly designed studies and improper model selection.

Thanks are due Jeffrey M. Lohre, M.A. and Patricia L. Garvey, Ph. D. for assistance in preparing this manuscript. The opinions expressed herein are those of the author and do not reflect the policies or opinions of Baxter Healthcare Corporation.

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