Preclinical Animal Models

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Topic Relevance by Timeline

Summary

- Animal models can support and develop medical product development during the nonclinical phase.
- Well-designed animal models can address regulatory safety concerns and can provide further de-risking during product validation.
- Assessing minimum viable products and prototypes in animal models can improve quality assurance and compliance structure.
- Developing a roadmap for product innovation strategies (regulatory, reimbursement) is essential in order to avoid unnecessary preclinical testing.
- Involving end users in product development is critical for the success of the medical device in the market.
- Animal studies can provide insight and value in the preparation of the regulatory submission.

Introduction

The purpose of preclinical animal testing is to provide reasonable evidence prior to early feasibile testing in humans and human clinical trials to demonstrate that novel technologies and therapies are safe and effective. Contacting prospective end users or Key Opinion Leaders (KOLs) during the preclinical phase is critically important and can provide insight and value for the potential medical device. It allows to align the technology with the unmet clinical need. Once an academic entrepreneur has focused on the specific problem the product will address, the next step is to define the intentional use of the medical device and its indications for use (Speer). The intended use is the general purpose of the device (what the academic entrepreneur claims the device actually does); the indications for use describe the condition that the device will diagnose, treat, or prevent, as

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well as the target patient population (Speer). The intended use and indications, in essence, describe the problem the academic entrepreneur has set out to solve and it must align with an unmet clinical need to successfully create value for the medical field downstream (value-based health care system). They are important because a key part of the product development process will be dictated by how the medical device will be classified by regulatory bodies. That classification is directly related to the time and money required to bring the product to market. Furthermore, defining the intended use and indications for use will help an academic entrepreneur start to establish the design controls and risk management.

Safety and efficacy data from preclinical animal models are an integral part of medical device development and necessary to make these decisions. This can help determine if the device is effectively solving an actual problem before moving on to costly human trials. Academic centers provide unique resources, often housed in the affiliated veterinary medicine schools, that can assist academic entrepreneurs in filling this preclinical void. Veterinary medicine schools usually include veterinarian faculty and staff with skills in product development for preclinical studies. Veterinarians can assist with a broad range of services, from product development to any regulatory/pivotal studies that are needed for good laboratory practice compliance for regulatory filings.

Elements to Consider for the Animal Study

In the process of designing preclinical animal research, an academic entrepreneur should provide a rationale for the selection of particular animal models for the study. It is important that the selected animal model serve as a test platform that offers the best physiological attributes to simulate the human clinical trials (Table 1). The Food and Drug Association (FDA) recommends that the elements of risk analysis and limitations of the animal model be addressed by describing the similarities and differences between the selected test platform and humans for utilizing device implantation; the surgical technique and location of device insertion in the animal model and in humans; and size-appropriate and anatomically appropriate barriers between the animal model and humans.

The animal studies for medical devices should be designed to better characterize the likelihood that a new therapeutic will be successful and will improve the success rate of clinical trials. An academic entrepreneur should conduct preclinical animal testing with the objective of studying the risks that are predicted from the design of the device, any known risks of the device type, and any new risks that may have emerged in prior investigations. The animal study protocol should recapitulate the human clinical trials as much as possible by encompassing steps from the preparation of the device to device placement and all the way to device withdrawal. In addition, medical devices can cause mechanical or biological stresses when placed in vivo. Therefore, it is important to identify physiological response variables on the body, to improve the chances of success for human trials.

Table 1. Selection of Biomedical Animal Models.

Animal models used in biological & functional studies	
Exploratory	Provides an understanding of fundamental biological mechanisms (Example: a novel animal model of aging, particularly for identifying genes and biochemical pathways regulating longevity)
Explanatory	Provides an understanding of complex biological problems (Example: cognitive and psychosocial animal models)
Predictive	Serves as a tool to discover and quantify the impact of investigative treatments whether for diseases or chemical toxicities
Animal models used in disease research	
Induced (or Experimental)	Experimentally created models either through surgical, genetic, or chemical modifications
Spontaneous	Genetically varied models which mimic the human condition
Transgenic	Induced models in which DNA is inserted into or deleted (knockout) from the genome of the animal
Negative	Animals that fail to react to a disease or chemical stimulus
Orphan	Opposite of negative models

Source: Adapted from Rand; Davidson et al.

During the preclinical development stage, the team should plan to have a pre-Investigational New Drug (IND) meeting with the FDA (Center for Drug Evaluation and Research). The goal of a pre-IND meeting is to receive confirmation from the FDA that the product development plan and future clinical trials are acceptable. To make the meeting effective, the team should try to focus on a specific regulatory or scientific issue. Pre-IND meetings will provide guidelines for initial IND submission at the end of the preclinical development process and can also reduce a product's time to market (see the chapter "FDA Drug Regulation: Investigational New Drug Applications").

Case study: Intervertebral disk/Nucleus pulposus devices

For these technologies the 510(k) approval process was often chosen (see the chapter "FDA Device Regulation: 510(k), PMA"). Sponsors often had to demonstrate substantial equivalence of their product regarding the safety profile using large animal models. Many of these technologies fell short demonstrating clinical efficacy in human patients with back pain. One important aspect here is to recognize the limitations certain animal models exhibit. For example, large animals do not overtly exhibit pain with intervertebral disc degeneration. They may be suitable to study the device

in a biological system for tissue compatibility, but fail to address one major clinical metric of alleviating pain; which is the single most important driver for clinical outcome in the human patient. As a result, the entire field has learned a tremendous amount in the past decade regarding intervertebral disc degeneration, pain generators and patient selection. Animal models have also become more rigorous. Intervertebral disc degeneration and back pain is a good example to leverage naturally occurring disease models that often demonstrate increased rigor and model fidelity like for example the dog.

Minimum Viable Products and Prototypes

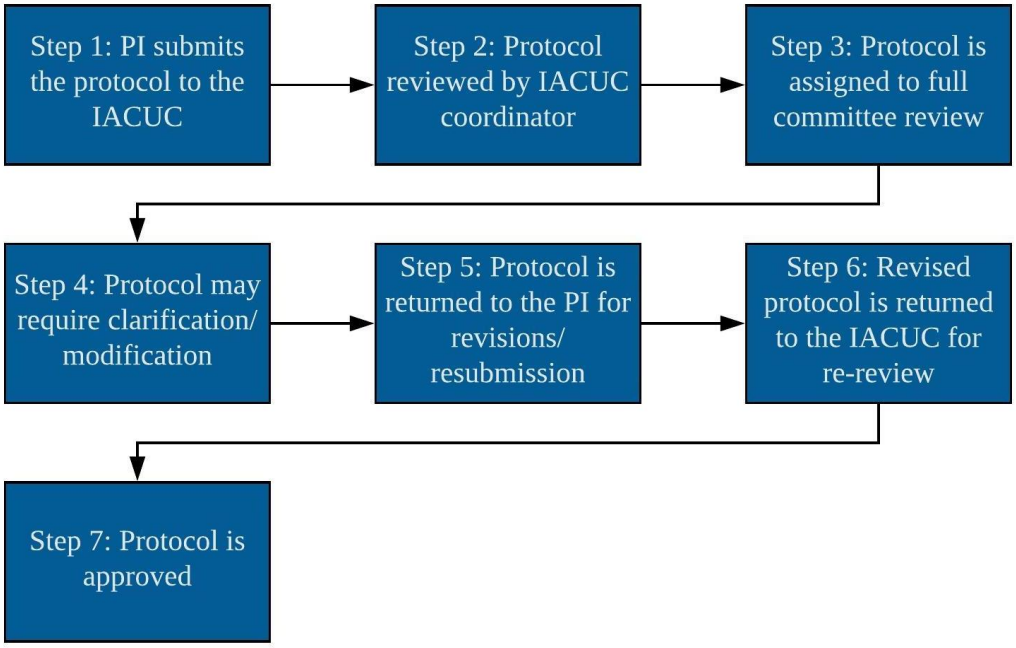
Animal testing using minimum viable products (MVPs) and prototypes are important for developing medical devices. Product development is comprised of several phases, and each of these phases can be considered as an MVP. In the initial phase, an idea or concept can be considered the first MVP. The next step is to define the intended use and involve end users; in this scenario, the MVP becomes a proof-of-concept prototype (see the chapter “Rapid Prototyping Strategies”). This step is essential since it proves invaluable insight into product development efforts. The process continues, with each MVP evolving as product development progresses toward production; with each MVP, it is crucial to include end users to provide feedback. Engaging end users, even in the early phases, will help ensure the developed product’s success in the market (see the chapter “Conducting Insightful Market Research”).

When going through the phases of evolving MVPs, the FDA recommends that the animal research team include skilled veterinary clinical experts in order to detect and resolve adverse outcomes. It is also recommended to involve investigators with a range of expertise, including human, clinical, and veterinary pathologic fields. Selecting qualified personnel and allocating sufficient resources is essential for monitoring and predicting the possible risks of the MVPs.

Testing MVPs in Animals

In the development of medical devices, earlier stages usually proceed relatively quickly. However, later stages usually require design verification and validation steps, so development slows accordingly. Verification and validation often involve numerous testing activities, and this is a point in product development when expenses start to increase exponentially. Therefore, it is important to spend a sufficient amount of time defining design inputs in earlier phases since they are the key to producing successful MVPs. Also, using prototypes as mini-bench tests to define design inputs and to establish verification/validation methods is advantageous.

Figure 1. Typical IACUC Review Process.



Preclinical animal testing can be done at any of these stages. Consulting with a preclinical testing program (e.g., the Institutional Animal Care and Use Committee, IACUC) can be helpful for developing a regulatory entry strategy (National Research Council (US) Committee for the Update of the Guide for the Care and Use of Laboratory Animals; Office of Laboratory Animal Welfare (OLAW), National Institutes of Health) (Figure 1); a sample of the University of Pennsylvania's IACUC documents can be viewed here: iacuc.upenn.edu. They may be able to recommend which animal to use (e.g., dog vs. sheep vs. pig, etc.; Table 2), which pathological model to use (e.g., naturally occurring disease model vs. induced disease model), parameters that need to be considered (e.g., safety or efficacy, etc.), and how to clarify the budget and milestones in order to satisfy regulatory requirements and the goal of the project. They can also be helpful in designing an appropriate environment that allows animals sufficient access to food and water, reducing background stress that could adversely affect the interpretation of study results, and observing/monitoring recovery after surgical procedures by providing intensive care treatments (e.g., intravenous medications, ECG monitoring, and temperature/humidity adjustments) according to regulatory guidelines (National Research Council (US) Committee for the Update of the Guide for the Care and Use of Laboratory Animals).

Design Controls and Risk Management

In the process of developing MVPs, it is critical to have written documentation of each version. This is the essence of risk management and medical device design controls (Speer). In the early phases, MVPs guide an academic entrepreneur toward what is important about the product as it

relates to end users. Once the academic entrepreneur has a proof-of-concept MVP, they can use this to establish and define design inputs. Design inputs are the foundation of the entire product development effort, setting the stage for future development activities and directly influencing any design verification/testing one plans on performing.

In preclinical animal research, the FDA recommends that the methods and materials utilized for the assessment of medical devices be similar to those utilized in humans. It is important to include adequate controls to minimize experimental variables and errors. In disease models, background levels of disease and psychological stress should be controlled as much as possible to generate data that can support the safety and performance of a medical device and obtain predictive outcomes. In addition, when considering the number of animals needed, it is important to decide which disease model to use (e.g., naturally occurring disease model vs. induced or experimental disease model). The naturally occurring disease model provides heterogeneity of cohort and increased generalizability—allowing for an effective and less expensive study. An induced disease model can be more expensive since animals need to be managed in the lab for the duration of the experiment. The FDA also recommends that study animals be monitored to assess possible risks posed by the device, using a post-mortem evaluations (e.g., micro-CT, light and scanning electron microscopy, histopathology).

Table 2. Animal Species Used in Biomedical Research.

Species	Advantages	Disadvantages
Flies 	Small, short generation time	Not vertebrates
Fish 	Short generation time, clear embryos	Not mammals
Mice 	Mammals, inexpensive, easy to handle, relatively small, many genetic tools available	Not primates
Rats 	Same as mice but larger	Fewer genetic tools

Rabbits		Nonaggressive, easy to handle, widely bred, economical compared to other larger animals, short vital cycles	Fragile bone structure, fewer genetic tools
Dogs		Outbred species, large	Costly, pets, ethical issues
Pig/ Minipig		Close analog to humans (80-90% of organ system corresponds to humans), early onset of tumors	Expensive to procure and maintain
Sheep /Goat		Long life expectancy, easy peritoneal catheter insertion,	Difficult and expensive breeding, large time frame for obtaining results
Horse		Large defects similar to humans, naturally occurring defects, similar biomechanics, presence of melanomas	Expensive to acquire and maintain, difficult to perform MRI/CT imaging due to size
Nonhuman primates		Similar to humans, large	Costly, ethical issues

Source: Adapted from
http://www.nabr.org/biomedical-research/laboratory-animals/species-in-research/

Product Innovation Strategies: Product-Driven vs. Value-Driven

There are two popular strategies for product innovation—product-driven and value-driven (Figure 2). For a product-driven strategy, one identifies the technology first, then assesses it as a solution for a problem. In contrast, for a value-driven strategy, one identifies the problem first, then makes the technology that serves as the solution. For medical device product development, especially in an academic center where a researcher may have done years of work evaluating a specific technology, the product-driven strategy is a more conventional and traditional approach. End users are

involved in this approach, but usually only in the late stages of the product development process. This carries significant risks, however, in that the technology may not meet end users' needs; to mitigate this risk, the opinions and feedback of end users evaluating a prototype device are invaluable. Therefore, involving end users from the beginning of product development, starting with the preclinical phase, can increase the success rate of the product in the market. In part to address this issue, value-driven approaches, such as the Stanford Biodesign model, have also been proposed. These can be more challenging for academic researchers, though, as they are often not beginning with a technology tabula rasa.

Figure 2. Product-Driven vs. Value-Driven Development Strategies.

PRODUCT-DRIVEN (CONVENTIONAL) STRATEGY:

VALUE-DRIVEN STRATEGY:

Case Study: Anti-infective technology

Involving KOLs (Key Opinion Leaders and clinicians) is important as conventional wisdom about diseases and what patients and providers want can often be poorly aligned with the clinical value proposition. For example, a polymer carrier matrix impregnated with an antimicrobial was developed as an anti-infective technology. The development team chose one specific antibiotic as the antimicrobial of choice without extensive KOL input which ultimately limited the clinical value proposition. However, by the time the product development team had end user feedback, the technology was too far advanced for them to make adjustments. In general, the business model to bring anti-infective technologies to market is broken. The current regulatory landscape requires enormous financial investments by product developers including clinical trials. Furthermore reimbursement for these clinically unproven technologies can be difficult which further decreases the appetite for industry to innovate in this space. This space is a good example to emphasize that regulatory clearance is not the only high risk metric in product development and receiving a reimbursement code is equally important towards an economically viable product (see the chapter "Reimbursement Strategies and CPT Codes for Device Development").

Preparation of Regulatory Submissions

When preparing regulatory submissions, consider using Europe as an initial market if the FDA's regulatory constraints for the proposed device are significant and make preclinical data challenging. Starting in Europe is the classical model for many U.S.-based companies, and one could present the clinical trial data from use in Europe to support an FDA approval application. In Europe, safety data are required, but one does not need to have a large animal study prior to human use, unlike in the U.S. Europe is curtailing the use of animals in biomedical research and focusing more on safety than efficacy, while in the U.S. efficacy and safety are both key, and a large amount of data is required. Another potential option is development in China—this can be easier if working with a Chinese partner. Chinese regulatory agencies are also receptive to safety and efficacy data collected outside of China.

For regulatory submissions, the FDA recommends including all relevant information collected from animal research, not limited to the following: the rationale for the model selection, the similarity of the selected model compared to humans, and the general animal study methodology used. In addition, it is important to include the rationale for the transition from the pilot, validation, or proof-of-concept studies to pivotal animal studies, as this information provides an understanding of how device safety was assessed. If any design changes have been made to the device, they should also be described in the regulatory submission, and there should be a performance report of the device across multiple studies.

Conclusion

Preclinical animal testing is a shared responsibility in which academic researchers, the pharmaceutical industry, regulatory authorities, and ethics committees (e.g., IACUCs) all play a part. Recently, a number of recommendations and guidelines (see Resources 1 and 4) have been published to encourage more accurate use of animal models. Using these guidelines, researchers must make sure they are using animals in the best possible way to make progress in the treatment of human diseases. Validation is critical for that reassurance, and preclinical animal studies should be thoroughly monitored for compliance with these guidelines. This not only limits the mistreatment of animals but also produces consistency and thus increases the potential success rate of the medical device in clinical trials as well as in the market.

Resources

1. Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research. "Product Development Under the Animal Rule." FDA-2009-D-0007, Food and Drug Administration, 6 Oct. 2019, http://www.fda.gov/regulatory-information/search-fda-guidance-documents/product-development-under-animal-rule. This document provides

helpful guidance that explains regulatory considerations, general expectations, and essential elements in animal studies.

2. To get a general overview of preclinical animal research and have a clear understanding of pathophysiological differences between animals and humans, refer to the following two papers:
    a. Everitt, Jeffrey I. "The Future of Preclinical Animal Models in Pharmaceutical Discovery and Development: A Need to Bring in Cerebro to the in Vivo Discussions." *Toxicologic Pathology*, vol. 43, no. 1, Jan. 2015, pp. 70–77, 3145 doi: 10.1177/0192623314555162.
    b. Subramani, Baskar, and Sadananda Rao Manjunath. "Preclinical Research: A Rise or Dawn." *Pharmacy & Pharmacology International Journal*, vol. 6, no. 1, MedCrave Publishing, Jan. 2018, pp. 62–65.
3. Reproducibility and validation of animal models are described in detail in these two articles:
    a. Varga, Orsolya E., et al. "Validating Animal Models for Preclinical Research: A Scientific and Ethical Discussion." *Alternatives to Laboratory Animals*, vol. 38, no. 3, June 2010, pp. 245–48, doi: 10.1177/026119291003800309.
    b. Voelkl, Bernhard, et al. "Reproducibility of Preclinical Animal Research Improves with Heterogeneity of Study Samples." *PLoS Biology*, vol. 16, no. 2, Feb. 2018, p. e2003693, doi:10.1371/journal.pbio.2003693.
4. Center for Devices and Radiological Health. "General Considerations for Animal Studies for Cardiovascular Devices—Guidance for Industry and FDA Staff." Food and Drug Administration, July 29, 2010, https://www.fda.gov/regulatory-information/search-fda-guidance-documents/general-considerations-animal-studies-cardiovascular-devices-guidance-industry-and-fda-staff.

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https://olaw.nih.gov/resources/tutorial/iacuc.htm.

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Speer, Jon. *6 Development Steps to Fast-Track Your Medical Device's Path to Market*. 5 Feb. 2016, https://www.meddeviceonline.com/doc/six-development-steps-to-fast-track-your-medical-device-s-path-to-market-0001.

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