FOCUS

REGULATION

Three Rs of Animal Testing for Regenerative Medicine Products

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Considerations of animal welfare have spurred the design of “smarter” preclinical studies intended to ultimately benefit patients.

Preclinical testing with the use of animal models is important in the development of novel regenerative medicine (RM) products before first administration in patients. The U.S. Food and Drug Administration (FDA) implements the three Rs (3Rs)—reduce, refine, replace—for such preclinical studies in order to evaluate the safety and effectiveness of RM products. Here, I summarize some of FDA’s insights and efforts into executing the 3Rs in regulatory research, product review practices, and policy arenas for RM products.

SAFETY FIRST

RM products for a variety of disease and injury applications are beginning to move from the laboratory bench toward the patient’s bedside. According to FDA regulations, the sponsor of a clinical trial for an investigational new drug application (IND) should provide “adequate information about the pharmacological and toxicological studies… on the basis of which the sponsor has concluded that it is reasonably safe to conduct the proposed clinical investigations” (1). For sponsors of an investigational device exemption (IDE) application, the FDA may disapprove or withdraw approval of the IDE if the “device is intended for a serious disease or condition and there is insufficient evidence of safety and effectiveness to support such use…” (2). The design of preclinical studies is thus a critical component in the generation of appropriate and sufficient data to support the clinical development of an investigational medical product. Such studies can potentially serve to both illuminate and mitigate some of the risks to humans enrolled in clinical trials (Fig. 1).

As product development progresses, usually a combination of in vitro experiments and animal studies is needed to characterize the safety and effectiveness profiles of an investigational product. In the RM arena, these products are complex; many consist of multiple components, such as a biologic (a cellular product) and a device (such as a biopolymer scaffold for delivery of the biologic). Because cellular components range from stem cell–derived to functionally differentiated products from autologous, alllogeneic, or xenogeneic sources, potential safety concerns include undesired immune reactions and tumor formation. The scaffold complications can include bioactive degradation products and adverse effects to the tissue that surrounds the implanted device. Therefore, these RM products require multifactorial safety and effectiveness profiles.

FEDERAL REGULATION OF ANIMAL STUDIES

The Public Health Service (PHS) and thereby FDA’s Center for Biologics Evaluation and Research (CBER) and the Center for Devices and Radiological Health (CDRH) adopts the U.S. Government Principles for the Utilization and Care of Vertebrate Animals Used in Testing, Research, and Training (the Principles) (3) for preclinical studies that involve animals. Therefore, when performing or contracting animal research for a given product, prospective clinical sponsors should adhere to the nine Principles in (3)—which include minimizing pain and distress, employing trained animal-care personnel, and using the fewest possible animals and alternatives to animals when appropriate. Another important publication, the Guide for the Care and Use of Laboratory Animals (the Guide) (4), provides detailed guidance on implementation of the Principles in (3) and the proper and humane care of laboratory animals. Any PHS-funded research [such as studies that rely on grants from the U.S. National Institutes of Health (NIH)] must be conducted within the boundaries of the Principles and the Guide, which are included in FDA guidance documents (5–7). In December 2010, FDA issued an advance notice of proposed rule-making (ANPRM) (8) to advise the public of its intention to amend the regulations for Good Laboratory Practice (GLP) for Nonclinical Laboratory Studies (9) so as to address animal welfare.

THE THREE Rs

Another way that FDA encourages implementation of the nine Principles is by practicing the 3Rs when animals are used in preclinical studies as part of a medical–product development program. First proposed by Russell and Burch in 1959, the 3Rs provide a strategy for reduction, refinement, and replacement in animal testing, and are an internationally accepted (10) approach for sponsors and investigators to apply when using animals in their preclinical studies. According to the Guide, the 3Rs are defined as follows: (i) Reduction refers to methods that minimize animal use and enable researchers to obtain comparable amounts of information from fewer animals or to obtain more information from the same number of animals without increasing pain or distress. (ii) Refinement refers to methods that minimize or alleviate potential pain and distress and enhance well-being for the life of the animal. (iii) Replacement refers to methods that avoid the use of animals by replacing them with other systems, such as cells or lower organisms.

FDAs strong endorsement of strategies to implement the 3Rs when evaluating the safety and effectiveness of a RM product is evident in FDA regulatory research, review practice, and policy.

3Rs IN REGULATORY RESEARCH

FDA is committed to advancing regulatory science through the development of new tools, standards, and approaches to assess the safety, efficacy, quality, and performance of FDA-regulated products. One way FDA is advancing regulatory science is through the Tox21 collaboration (www.epa.gov/nct/Tox21), which works to research, develop, validate, and translate innovative chemical testing methods that characterize toxicity pathways. The Tox21 collaboration has led to development of a new high-speed robotic screening system that can test 10,000 different chemicals for potential toxicity. Use of this robot may lead to a reduction in animals used for toxicity testing of RM products.

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Both CDRH and CBER have multiple ongoing research projects that seek to find alternative methods and systems for testing the safety of RM products. For example, the Office of Science and Engineering Labs (OSEL) at CDRH investigates use of computational models to predict cardiovascular device behavior (degradation, fatigue, wear) after in vivo administration (www.fda.gov/AboutFDA/CentersOffices/CDRH/CDRHTechnicalReports/ucm274152.htm). One of the ongoing projects of the Office of Cellular, Tissue and Gene Therapies (OCTGT) at CBER involves biomarker development to predict in vivo biological and pathological responses to RM products. Data from research projects in these FDA centers are made available through presentations at scientific meetings, at public workshops, and in publications, increasing the potential impact these projects may have on expanding use of the 3Rs.

**3Rs IN THE REGULATORY REVIEW PROCESS**

RM product development requires a pyramid of preclinical assessments, starting with proof-of-concept studies and ending with pivotal safety studies, before use of the product in a patient population. The extent of the preclinical program for these products depends on the novelty and complexity of the biological and device components and the planned clinical use. CBER/CDRH encourages early communication so as to discuss the preclinical program envisioned for an RM product by its sponsor. The pre-submission pathway (the pre-IND or pre-IDE meetings) provides an effective means to achieve this goal. These interactions enable sponsors to interact with subject-matter experts—in pharmacology, toxicology, veterinary medicine, chemistry, biomedical engineering, materials science, clinical medicine, and statistics—on the various components of their RM product and to receive comments, questions, and recommendations from CBER/CDRH on the proposed preclinical studies, with implementation of the 3Rs wherever feasible and appropriate from a scientific and regulatory perspective. Thus, FDA encourages the sponsor to review the Guide and the Principles before the presubmission meeting and to discuss possible modifications to preclinical testing programs in these early interactions in order to ensure that researchers conduct a high-quality, appropriately sized GLP study that will not need to be repeated, reducing animal use.

Selection of appropriate animal species is probably the most important aspect of a preclinical testing program. First, the species used should be responsive to the biological component being introduced. For RM products, considerations include the nature of the cellular-product component, the anatomical site of product administration, the total surface area of the finalized device component, and required study endpoints. Choosing an animal model of disease or injury that to some extent recapitulates the pathogenesis of the given disease or injury in humans may also help to fulfill certain aspects of the 3Rs. Whenever feasible, CBER/OCTGT recommends the use of hybrid pharmacology and toxicology studies in animal models of disease or injury—those that encompass the assessment of safety and effectiveness endpoints relevant to the proposed clinical indication and to the investigational RM product. This strategy allows for the collection and evaluation of multiple data points intended to capture dose-activity and dose-toxicity profiles in the minimum number of animals deemed necessary. Such designs can provide strong support for fulfilling the 3Rs.

FDA also weaves the 3Rs into their regulatory review practice by encouraging investigators to increase the frequency with which they assess clinical parameters in animal studies. As suggested in a CDRH guidance document (5), this can be accomplished by following current standards of record-keeping in veterinary medicine, such as the subjective/objective assessment and plan (SOAP) format. This practice ensures that observed adverse findings are managed in as timely a manner as possible in order to reduce pain and distress, benefiting the animal’s welfare. Furthermore, by closely monitoring the animals, such findings can be appropriately investigated to determine a possible cause, which in turn can inform necessary changes to the preclinical study protocol (such as reduction of dose, inclusion of additional monitoring, or early termination of the study) and can help to guide in design of the initial safety trials in patients.

Finally, another way FDA incorporates the 3Rs into its regulatory practices is through leveraging known and accessible data (from published literature or other sources) on particular products to reduce the size and number of animal studies. This can be particularly useful for the device component of the RM product. For example, if the toxicity of a scaffold implanted in a particular anatomical site or for a particular anatomical use is well understood, then scaffold toxicity studies in animals may not be necessary or may be reduced in scope.

**3Rs IN REGULATORY POLICY**

FDA also actively promotes the 3Rs through regulatory policy and outreach endeavors, such as the promotion of potential alternatives to animal testing. In addition to outreach through participation at scientific meetings, FDA engages in collaborative programs and
initiatives such as the Interagency Center Coordinating Committee on the Validation of Alternative Methods (ICCVAM; http://iccvam.niehs.nih.gov). ICCVAM’s directive is to promote the regulatory acceptance of new and scientifically valid toxicological tests that protect human and animal health while incorporating the 3Rs. Since 1998, this interagency group has contributed to national and international acceptance of 42 alternative safety-testing methods, 24 of which do not involve animals.

As representatives of FDA, CBER and CDRH also actively participate in the Multi-Agency Tissue Engineering Science (MATES) Interagency Working Group. Established in 2000 under the Subcommittee on Biotechnology of the National Science and Technology Council (NSTC), the primary purpose of MATES is to provide a platform between the member federal agencies for interaction and exchange on the science and technologies of tissue engineering (www.tissueengineering.gov). One of the ongoing activities of this group involves the organization of workshops on safety-testing methods that are possible alternatives to animal use.

Beginning in 2010, NIH and FDA partnered to advance public health through an initiative designed to accelerate the process from scientific discovery to availability of medical therapies for patients through the Advancing Regulatory Science (ARS) Initiative. Part of this initiative involved establishment of the Advancing Regulatory Science through Novel Research and Science-Based Technologies grant program (http://grants.nih.gov/grants/guide/rfa-files/RFA-RM-10-006.html). The goal of this program is to fund research on the applicability of novel technologies to support improved evaluation of product safety, quality, effectiveness, and manufacturing throughout the product life cycle. In the first round of funding, one of these grants was awarded to a project that is investigating integration of organ-on-chip microdevices to produce a heart-lung micromachine. This innovative product combines microfabrication techniques from the computer industry with modern tissue-engineering techniques in order to replicate the complex physiological functions and mechanical microenvironment of a functional heart and lung. According to the grant, the goal of this microdevice is to provide accurate and immediate measures of the efficacy and safety of inhaled drugs, nanotherapeutics, and other medical products on integrated heart and lung function (http://projectreporter.nih.gov/project_info_description.cfm?aid=8068443&icde=0). The success of this project may lead to a reduction in, and perhaps replacement of, animal use for certain safety tests. This example illustrates how consideration of the 3Rs has spurred efforts to design “smarter” preclinical studies intended to ultimately benefit the patient.

REFERENCES AND NOTES

Acknowledgments: The author thanks M. Serabian (FDA/CBER/OCTGT), R. McFarland (FDA/CBER/OCTGT), V. Hampshire (FDA/CDRH/ODE), and M. John (FDA/CDRH/ODE) for their assistance in preparing this commentary.


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Sci Transl Med 3, 112fs11112fs11,
DOI: 10.1126/scitransmed.3003394

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