Chapter XXXI: Product Development and Regulatory Considerations in Delivering Radiation-Nuclear Medical Countermeasures

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Introduction

Victims of a radiological or nuclear event will require considerable medical care for burn or blast injuries, but also for the effects of ionizing radiation or internal contamination. Much of these treatments will be standard medical management, such as fluid replacement, nutritional supplementation, antibiotics or transfusions (*1*), but other treatments are needed to mitigate damage to sensitive organs, such as the hematopoietic and gastrointestinal systems, lungs or kidneys.

Many organizations such as pharmaceutical companies, national laboratories and academic groups, are developing medical countermeasures (MCMs) that can improve outcomes in exposed individuals. These MCMs could be products approved for other indications or products developed specifically for a radiation indication. In either case, the MCM will need to follow the regulatory pathway for the development and approval of drugs and biologics by the United States Food and Drug Administration (FDA). There are three regulatory pathways (traditional, accelerated, and animal rule). In this chapter, primarily the traditional and animal rule pathways will be described with a focus on the unique aspects of developing MCMs for radiological or nuclear indications. Although not a pathway to approval, an MCM could be available for use under an Emergency Use Authorization (EUA); the EUA mechanism will also be briefly discussed.

Government Needs

Requirements

The Department of Health and Human Services (HHS), through its Public Health Emergency Medical Countermeasures Enterprise (PHEMCE), has developed a Strategy and Implementation Plan (SIP) that outlines the coordination of federal government activities to develop MCMs that could be used in a public health emergency (*2*). The PHEMCE considers MCM needs based on potential scenarios and the types of injuries that could be encountered as a result of a radiation or nuclear event, the concept of operations, and the ability to sustain a robust drug development pipeline and a ready supply of a given therapeutic. In Objective 1.3, the 2017 SIP describes a robust and sustainable pipeline that "includes consideration of viable commercial markets and/or routine public health applicability." There are two advantages of having a viable commercial market: 1) a business model with steady income rather than periodic procurements is more sustainable, and 2) the general use commercial indication may allow the sponsor to use the

human safety data for the radiation-nuclear marketing application and the general use human efficacy data may be supportive for the radiation-nuclear indication.

FDA Animal Rule

In the United States, approval of drugs and biologics, including cellular products, is granted through the FDA's Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER). The approval process for drugs and biologics, under any regulatory pathway, includes evaluation of safety and efficacy. Under the traditional and accelerated approval regulatory pathways, these are evaluated in adequate and well-controlled clinical trials in patient populations; however, because intentionally exposing people to lethal radiation is unethical, testing efficacy in patients cannot be done. Because of this limitation, in 2002 the FDA developed the "Animal Rule" as a regulatory pathway to allow for approval of drugs and biologics when clinical testing for efficacy in a patient population is not ethical or feasible. The basic idea behind the Animal Rule is that adequate and well-controlled efficacy studies performed in animals can serve as surrogates for human clinical efficacy trials.

The Animal Rule regulations can be found in 21 CFR 314.600 – 314.650 for drugs and 21 CFR 601.90 – 601.95 for biologics. These regulations cover "products that have been studied for their safety and efficacy in ameliorating or preventing serious or life-threatening conditions caused by exposure to lethal or permanently disabling toxic biological, chemical, radiological, or nuclear substances." The regulations define the applicable products for approval under the Animal Rule to be "products for which: Definitive human efficacy studies cannot be conducted because it would be unethical to deliberately expose healthy human volunteers to a lethal or permanently disabling toxic biological, chemical, radiological, or nuclear substance; and field trials to study the product's effectiveness after an accidental or hostile exposure have not been feasible." It is important to note that the Animal Rule cannot be used if efficacy for a particular indication can be demonstrated in human clinical trials. It is important, then, for a developer to establish early in the development process whether the regulatory path will depend on approval under the Animal Rule. This determination can only be made in consultation with the FDA, and the sponsor should engage in discussions with the Agency before filing an Investigational New Drug (IND) Application.

The Animal Rule is often described as having four tenets, all of which must be satisfied before a product can be approved. First, the pathophysiological mechanism of action of the injurious substance and how the product will prevent or treat the toxicity arising from the insult need to be reasonably well-understood.Second, efficacy "in more than one animal species expected to react with a response predictive for humans, unless the effect is demonstrated in a single animal species that represents a sufficiently well-characterized animal model for predicting the response in humans" needs to be demonstrated. Third, the endpoint of the animal efficacy study must be related to the human endpoint, that is generally mortality or prevention of major morbidity. Fourth, there needs to be adequate pharmacokinetic or pharmacodynamic information to allow for the selection of an effective dose in people.

When developing a product for approval under the Animal Rule, it is important to plan studies to fulfill all these requirements. The natural history of the disease or condition in the animal species chosen should demonstrate the key features of the disease or condition in humans, and the drug's effect in the animal species is expected to be predictive of the response in humans. In addition, efficacy studies described in 21 CFR 314.610(a)(3) that support approval are expected to have as a primary endpoint mortality or major morbidity. These efficacy studies may also include secondary endpoints that could support mechanism of action or provide pharmacodynamic information that would help allow for a selection of an efficacious dose in people. It is important, also, that approval is based on "adequate and well-controlled animal studies" and may be supplemented by data from other human efficacy studies in relevant indications.

More details regarding the use of the Animal Rule are provided later in this chapter.

Product Development

General Product Development

In the United States, the FDA determines which drugs or biologics can be approved for use, based on a review of available evidence. Because of this, medical product developers must follow the statutory requirements in the Federal Food, Drug and Cosmetic Act (FDCA) for drugs, the Public Health Service (PHS) Act for biologics, and the implementing regulations that have been developed. Interactions between product developers and the FDA take place predominantly during the Investigational New Drug (IND) application stage, which is the period when the clinical testing and chemical characterization of an investigational product occurs. The NDA (New Drug Application) or BLA (Biologics License Application) stage is when FDA reviews the data submitted to support approval or licensure, respectively.

In order for a clinical trial involving an unapproved drug or biologic to begin, the FDA must be assured that the clinical protocol is adequate and that safety of the study subjects has been assured. The requirements for an IND application are described in 21 CFR 312 Subpart B: Investigational New Drug Application (IND) 312.20 – 312.38. An IND will contain the results of pharmacology and animal safety studies, as well as details on the product's manufacturing. The pharmacology and toxicology studies in animals or *in vitro* that are used to support an application are expected to be adequate for data inspection and study reconstruction. This generally means that they are conducted under Good Laboratory Practice conditions (21 CFR Part 58).

The path to approval is long and most of the candidate drugs or biologics fail at some step along the process (*3*), but having a robust pipeline consisting of a number of candidates will enhance the chances of success. A preclinical researcher may only focus on efficacy in a given animal model, but other factors regarding the use of the drug or biologic product should also be taken into consideration by developers. Safety, ease of administration, stability, manufacturing scalability, intellectual property, and market share, for example, are important considerations for determining whether a given project is successful. All of these factors, which may seem

peripheral to the researcher, are important and satisfying these needs takes additional funding and expertise. Because of the need to use scarce resources efficiently, it is important, then, to set up decision points along the drug development pathway. A brief description of a traditional or accelerated drug development pathway is described below.

Preclinical efficacy and safety studies are important to establish the optimal dosing of the product and the methods by which the product and any impurities or metabolites can be measured in solution or in biological tissues. Results from the animal safety studies will identify what toxicities could be expected in people and the pharmacokinetics of the product, which are necessary to guide dosing in people. It is important to be able to uncover a product's adverse effects, even if the product has a very favorable therapeutic index, so that these toxicities can be anticipated and monitored in a clinical trial. At this time in the development process, assays and specifications for the identity and purity of the manufactured product can be determined, and a manufacturing process established. The standard animal safety tests and guidelines for manufacturing, as well as guidelines for clinical protocol development and monitoring, are listed in 21 CFR 312.23.

Clinical trials are generally performed in phases: Phase 1 – safety and pharmacology, Phase 2 – efficacy in a relatively small number of patients, and Phase 3 – efficacy in a sufficiently large patient population. Phase 1 trials are normally performed in healthy individuals, but these trials may include patients who have the specific disease for which the product is directed. In the Phase 1 trials, the candidate drug's pharmacokinetics are determined. Because safety is also considered in the larger Phase 2 and Phase 3 trials, the number of patients in most Phase 1 trials is often limited. Phase 2 and 3 trials are designed to show benefit to the patient and eventually become the basis for demonstration of efficacy. Because a product with limited clinical experience in human subjects may have an inadequate safety database, a more extensive Phase 1 program may be required.

Product Development for Radiation/Nuclear Indications

Traditional product development has its own pitfalls and challenges, but the framework for the sets of studies that demonstrate safety and efficacy and that could support approval or licensure has been established for many product types and disease paradigms. These precedents, however, are not as firmly established for radiological or nuclear (rad/nuc) MCMs. For these, the Animal Rule may provide a development pathway, but its application to a product for a specific indication should be agreed upon by the FDA. Of particular importance is the guidance for industry *Product Development Under the Animal Rule* issued in October 2015 (*4*).

A laboratory or company that has a lead candidate or set of candidates may be seeking data and funding. There are organizations within the federal government that can provide data, funding, and advice; investigators and companies are encouraged to contact funding agencies such as the Radiation and Nuclear Countermeasures Program at the National Institute of Allergy and Infectious Diseases (NIAID) or the Biomedical Advanced Research and Development Authority (BARDA) within the Department of Health and Human Services. Early in the discovery phase,

an investigator will want to make sure that a patent position is established and should therefore partner with the organization's technology transfer office, which may also assist with partnerships that have the necessary resources and expertise for drug development. It is important to understand that generally the entity that submits applications to the FDA concerning the product development pathway is the pharmaceutical sponsor/manufacturer.

MCM candidates can be products that are being developed de novo for a rad/nuc indication or be drugs or biologics that are already approved or licensed by the FDA and are being repurposed for the rad/nuc indication. There are several advantages to repurposed drugs: costs of development can be lower since many of the safety studies have already been performed (*5*), and these products could be available using a vendor-managed inventory model.

Test Case: G-CSF Approval

Neupogen® (filgrastim, G-CSF) and Neulasta® (peg-filgrastim, peg-G-CSF) are examples of successful repurposing of existing products. Both products, which accelerate neutrophil recovery in neutropenic patients, were approved for patients with hematopoietic subsyndrome of acute radiation syndrome (H-ARS) using the FDA Animal Rule with adequate and well-controlled studies performed in Rhesus macaques (*Macaca mulatta*), supporting studies performed in mice, and the clinical experience in millions of patients. (*5*)

From the FDA-approved package inserts:

> NEUPOGEN is a leukocyte growth factor indicated to
>
> - Increase survival in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Syndrome of Acute Radiation Syndrome) (1.6) (*6-8*)
>
> Neulasta is a leukocyte growth factor indicated to
>
> - Increase survival in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Subsyndrome of Acute Radiation Syndrome). (1.2) (*7, 8*)

The Blue Ribbon Panel that drafted the H-ARS Treatment Guidelines (*1*) suggested the use of these leukocyte growth factors (these G-CSF products as well as GM-CSF) to manage patients exposed to lethal irradiation and expected to have hematopoietic system damage. Although these products could have been considered for use under an EUA (see below), a labeled indication based on the Animal Rule was much preferred, since use would not depend on administrative processes during an emergency. For this reason, in 2005 NIAID began a collaboration with Amgen to approach the FDA to establish an agreement on a path towards approval of a colony stimulating factor for the treatment of H-ARS (*9*).In 2005, NIAID also awarded a contract for Product Development Support Services to the University of Maryland School of Medicine (UMSOM, PI: Thomas J. MacVittie), with the objective of providing support for medical countermeasure development. Among other activities, this contract was used to conduct the

studies and FDA provided the regulatory guidance to facilitate facilitate Amgen's submission of data needed to support approval of the new indication.

In 2007, Amgen ended its collaboration with NIAID, but through the UMSOM Contract, NIAID was able to continue to test G-CSF administration for efficacy. The FDA Animal Rule specifies that studies will be performed in "[m]ore than one animal species expected to react with a response predictive for humans," so it was important to characterize the animal models that would be used for the efficacy studies.

For Rhesus macaques, this important foundation was built at the UMSOM in a study in which the radiation dose-response relationship (DRR) under a medical management protocol was established (*10*). In this study, the primary endpoint was survival, but many secondary endpoints such as time-to-death, neutrophil-related parameters, infection, fever, etc., were measured to gain information that could demonstrate the extent of the injuries caused by ionizing radiation and provide possible parameters to show treatment-induced recovery. This model development study established the lethal doses (LD) of radiation that would result in various levels of lethality (30%, 50%, or 70%) over a given period of time (60 days): LD30/60, LD50/60, and LD70/60 at 7.06 Gy, 7.53 Gy, and 7.90 Gy, respectively, and demonstrated that the neutrophil and platelet kinetics, showing the loss of the cells, and the recovery, were not dependent on radiation dose within these limits.

In a study performed under Good Laboratory Practice (GLP) conditions at the UMSOM, Rhesus macaques were administered test article (Neupogen®) or control article (dextrose 5% in water) starting 24 hr after irradiation at 7.5 Gy (corresponding to the calculated LD50) (*11*). Because this was to be the adequate and well-controlled efficacy study that could fulfill the requirements of the FDA Animal Rule, bias was minimized using: animal randomization by the statistician prior to their transfer to study, euthanasia criteria that were designed to be as objective as possible, and blinding both the individuals providing animal care and those responsible for euthanasia decisions to the animals' treatment providing animal care and those responsible for euthanasia decision. To minimize the number of animals used in the study, a Data Monitoring Committee was established at NIAID and this committee was responsible for evaluating the survival and neutrophil count data at a pre-determined point in the study to make a recommendation for stopping the study due to efficacy or futility.

After 46 (24 treated, 22 control) animals were tested, the data showed that Neupogen treatment reduced 60-day mortality from 59.1% to 20.8%. This improvement in survival was associated with a decrease in neutropenia duration (*11*). It is important to note that besides the published data used to support the Neupogen efficacy under the Animal Rule, the Final Report also addressed adherence to GLP standards. Any planned excursions from the approved protocol were captured in amendments to the protocol. Any unplanned excursions from the protocol or Standard Operating Procedures (SOPs) were reported as deviations. Because the test article was diluted, identity and concentration were confirmed by HPLC and bioactivity assays. One of the side effects of Neupogen administration is splenomegaly, with possible splenic rupture. Because of this safety concern, splenic examination was incorporated into the necropsy protocol. NIAID

submitted the Final Report to the FDA under its preIND, who asked for additional analyses and tests. Because these results would be used to support a label indication, the facility and data were subject to FDA inspection to determine whether the study adhered to GLP standards.

At the same time that the NHP model was being characterized, the Indiana School of Medicine (PI: Christie M. Orschell), under subcontract to the UMSOM, characterized the C57BL/6 radiation mouse model (*12*). These studies established the LD levels when various antibiotics (or no antibiotics) were given in drinking water and the cellular kinetics in response to radiation. These studies also demonstrated the efficacy of Neupogen treatment, as survival was increased and neutrophil recovery was accelerated. Although these studies were not conducted under GLP conditions, Final Reports were submitted to NIAID's pre-IND.

In May of 2013, the FDA convened an Advisory Committee consisting of the combined Oncology Drugs Advisory Committee and the Medical Imaging Products Advisory Committee (*13*). At this meeting, the data from the NHP model development and Neupogen efficacy studies were presented, and the Committee voted on whether the animal data collected, along with supporting clinical data, supported the use of Neupogen to treat injury from a radiation exposure. In a 17-1 vote, the Committee agreed. After the Committee's determination, Amgen cross-referenced the NIAID-generated reports and along with thjeir own data analysis and the clinical experience with Neupogen, gained approval for the hematopoietic subsyndrome of acute radiation syndrome indication in March of 2015.

A similar NHP study was performed with Neulasta treatment. Again, the study was stopped early for efficacy as Neulasta treatment significantly improved survival of irradiated Rhesus macaques and accelerated neutrophil recovery (*7*). Amgen was given permission to cross-reference the report submitted to NIAID's pre-IND to gain Neulasta approval in November of 2015.

Emergency Use of Products for Radiation/Nuclear Indications

In the absence of an approved drug or biologic or when an approved alternative is unavailable, an MCM developer may consider submitting an Emergency Use Authorization (EUA) request to the FDA (*14*). The EUA "authority allows FDA to help strengthen the nation's public health protections against CBRN [chemical, biological, radiological or nuclear] threats by facilitating the availability and use of MCMs needed during public health emergencies." Under the EUA authority, "the FDA Commissioner may allow unapproved medical products or unapproved uses of approved medical products to be used in an emergency to diagnose, treat, or prevent serious or life-threatening diseases or conditions caused by CBRN threat agents when there are no adequate, approved, and available alternatives." (*15*)

FDA's general recommendations and procedures applicable to the authorization of the emergency use of certain medical products are covered in the FDA guidance for industry *Emergency Use Authorization of Medical Products and Related Authorities (15).* After the requisite determination and declaration have been issued, and after feasible and appropriate consultations, FDA may issue an EUA only if FDA concludes that the following four statutory

criteria for issuance have been met: the CBRN agent is capable of causing a serious or life-threatening condition, FDA's review of the available evidence concludes that the product may be effective, FDA's review concludes that the known and potential benefits of the product outweigh its known risks, and there are no adequate, approved, and available alternative products.

In advance of an emergency, an MCM developer (whether industry or government) may submit information about a given product as a pre-EUA package. This allows FDA to review the available data and assess the completeness of the EUA package prior to an emergency, ensuring more rapid decision-making at the time of an event. The pre-EUA package should follow the recommendations for a pre-IND or IND submission and should include information comparable to an FDA-approved package insert or instructions for use, known as "Fact Sheets" to be furnished to health care professionals or authorized dispensers and recipients of the product. Information that mirrors the requirements of the Animal Rule, such as mechanism of action, evidence of preclinical efficacy (including any animal efficacy studies), any relevant human data, and pharmacokinetic and pharmacodynamic data that would support a proposed human dose.

It is important to note that an EUA should not be considered a regulatory endpoint, but that a sponsor should continue development via the appropriate approval pathway and remain in communication with the relevant FDA review division.

Regulatory and Scientific Considerations

The test cases indicated above illustrate how the FDA Animal Rule can be used for drug development and result in approval, in this case for Neupogen and Neulasta for patients with the hematopoietic subsyndrome of acute radiation syndrome. As noted above, the FDA has published an industry guidance, *Product Development Under the Animal Rule*, that provides suggestions for organizations interested in product development for a CBRN indication . The first consideration is whether approval can be achieved using the traditional regulatory pathway. For many, if not all, drugs used to treat life-threatening radiation injury, studies could not be conducted in human subjects under the traditional drug development pathway as such studies would be unfeasible or unethical; therefore, the Animal Rule would be appropriate. The decision to develop a drug or biologic product under the Animal Rule regulatory pathway, along with a review of the development plan, should be established early with the appropriate FDA review division. In the example cited above, the model development and efficacy studies in NHP and mouse models were submitted to the FDA, in addition to justifications for the models, the primary and secondary endpoints, and justification for the human dose selection. It is important that the study endpoints should align with desired labeled indications and the FDA Animal Rule. The FDA-approved package insert for Neupogen, for example, states that Neupogen is indicated to "[i]ncrease survival in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Syndrome of Acute Radiation Syndrome)." The efficacy studies used to support this indication, then, incorporated survival as a primary endpoint, which is consistent with the Animal Rule endpoint of mortality or major morbidity.

The animal models chosen should reflect the injury seen in humans and the mechanisms of injury and recovery that a given product would treat. For example, myelosuppressive doses of radiation cause similar declines in blood neutrophil counts and similar recovery from radioresistant bone marrow stem cells in people (*16*) and NHPs (*10*). This fact, along with similar effects of G-CSF on neutrophil recovery allowed the NHP to be used as a well-characterized animal model for Neupogen. Although the drug dosing in mice needed to be adjusted to account for species differences, mouse efficacy data were submitted to support the Neupogen indication. The similarities in the natural history of radiation exposure in animals and the mechanism of action of G-CSF led to confidence that the treatment would be effective in humans.

The adequate and well-controlled studies used to support an indication should have sufficient documentation to allow a reviewer to ensure that the studies were performed according to the protocol and SOPs; therefore, it is essential that the organizations conducting these studies have adequate quality programs. One way to ensure the data quality and integrity is to follow GLP procedures (21 CFR Part 58). Any elements that cannot be conducted under GLP need to be indicated to the reviewing agency prior to study initiation, along with plans to ensure data quality and integrity of these elements.

Dose selection should be based on available pharmacokinetic and pharmacodynamic data and linked to doses used in human studies. Although allometric scaling may be adequate for small molecules, species specificity of biologics needs to be taken into account for dose selection. Various pharmacokinetic parameters (Cmax, t1/2) may vary among species; therefore, modeling will need to be used to show adequate drug exposure in patients. Dosing (route of administration, timing, formulation) should also mimic the human experience as closely as possible. This can be a challenge for pills/tablets/capsules or other *per os* dosing since patients are much more compliant for oral dosing than are animals that have been irradiated.

Two other considerations for studies performed under the FDA Animal Rule are statistical power and adequate animal care. It is important to select appropriate tests for primary and secondary endpoints; these tests will depend on the type of data that will be collected. The FDA Animal Rule states that the primary endpoint for the efficacy studies is "generally the enhancement of survival or prevention of major morbidity." The precise endpoint will be based on concurrence with the FDA. Secondary endpoints should support the primary endpoint and provide information on the mechanism of action. For example, in the Neupogen and Neulasta studies, the primary endpoint was survival, while neutrophil-related parameters supported the mechanism of these leukocyte growth factors. An adequate statistical plan will include animal number justification based on efficacy assumptions and the tests that show improvements in the primary and secondary endpoints. At a rudimentary scale, adequate veterinary care describes adherence to the Animal Welfare Act (AWA) as well as Public Health Service (PHS) standards. This adherence is documented by licensure (for the AWA) and the NIH Office of Laboratory Animal Welfare Animal Welfare Assurance, as well as accreditation by the Association for Assessment and Accreditation of Laboratory Animal Care, International (AAALAC). Because irradiation causes considerable injury to animals, veterinary care will be a part of the protocol and

interventions will normally be necessary, as per the protocol. Some interventions will be driven by an organization's Institutional Animal Care and Use Committee (IACUC) as part of an organization's normal veterinary care, others will mimic the expected clinical scenario, while others are necessary to show the injury in the affected animals.

Interventions that are a part of adequate veterinary care, established by an organization's IACUC, include analgesia or euthanasia. It is important that clear criteria be established for euthanasia, not only to best avoid or minimize suffering, but to reduce bias. Using objective criteria, such as well-characterized scales for observations or weight loss, along with adequate blinding, could be considered steps were taken to minimize bias. Depending on the species used, there are a number of interventions that approximate the clinical scenario, keeping in mind that resources could be stressed in a mass casualty situation. These interventions, which could include antibiotics, antivirals, or antifungals; fluid or nutrition support; or blood products, are best discussed with the FDA and the funding agency prior to initiation of the study. Currently, two leukocyte growth factors have been approved for ARS; therefore, consideration should be given to the possible use of these colony stimulating factors in the adequate and well-controlled animal efficacy study. The scale of medical management that mimics the clinical situation will vary among species. Rodents may only receive minimal intervention, because they cannot be monitored as readily as large animals and are susceptible to stress from handling. On the other hand, larger animals may receive interventions that more closely resemble what would be available for human patients. Other interventions, such as bone marrow shielding, or a manipulation of the radiation field to isolate specific organ systems, may be necessary to demonstrate system-specific injury or allow for recovery. Whatever interventions end up being used, their application and effects should be understood prior to the efficacy studies.

Animal models used in early-stage development (*17*) may vary from the animal models used for adequate and well-controlled studies used to support a label indication. These models should be discussed with the FDA to determine if these are adequate or how best to transition to other models. For example, exploratory studies may have included radiation to limited parts of the animal, such as abdomen or other parts of the GI system. These data, as well as clinical data in other indications, could be used as supporting data in a submission. It is important, however, to ensure that the submitted data are consistent and that they justify the claims made by the sponsor.

One variation of the regulatory strategy to be used under the FDA Animal Rule is the situation of radiation exposure via internal contamination, or exposure that can result from a radiological dispersion device ("dirty bomb"). Under most situations, damage to an exposed individual is characterized by continuous exposure to internalized radionuclides and as a result, may take years to manifest (*18*). Treatments, then, will most likely take the form of chelating agents that can accelerate the decorporation of radionuclides. In applying the Animal Rule to decorporation agents, the FDA has suggested through its *Guidance to Industry: Internal Radioactive Contamination – Development of Decorporation Agents*, issued in March 2006 (*19*), that efficacy in animals be based on the reduction of the whole-body committed radiation dose, which is calculated by measurement of the elimination of radioactive contaminants in urine and/or feces. Depending on the specific drug, the need and timing for safety studies in healthy human

volunteers should also be considered in the drug development plan. As is the case for all MCMs being developed for radiation exposure, the FDA should be consulted before an organization embarks beyond the discovery phase.

Conclusions

The development of products that can be used to prevent and treat a disease or injury is challenging and most promising products fail at various stages of development. A sponsor must demonstrate safety and efficacy of the drug or biologic using adequate and well-controlled studies to the satisfaction of the FDA. Failure can be due to safety issues, the failure to translate to the clinical setting (efficacy cannot be established), or because of business reasons (a market size that will not support a given product). Approval of medical countermeasures against radiation encounters different challenges since the market is specialized, and these products cannot be tested in real-world conditions. Various US government agencies have been tasked with stocking and maintaining a robust product development pipeline, and the experiences of these agencies in guiding sponsors through the drug development process and providing funding opportunities can assist researchers with promising products.

The FDA Animal Rule provides a pathway for approval or licensure, but because animal studies are surrogates of human studies, endpoints are more restricted than with traditional drug development. Independent of the traditional or the Animal Rule regulatory pathway used, the claims made by sponsors must be backed by solid evidence and conclusions need to be well-justified. Because of these challenges, a sponsor should communicate with organizations that have Animal Rule drug development experience, become familiar with the regulations and corresponding guidance documents, and communicate with the FDA and funding agencies early and often.

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