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Development of Drug Products for the Treatment of Acute Radiation Syndrome

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Brief Report

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Abstract

The Food and Drug Administration's (FDA) approval to market drug products for use as medical countermeasures, to prevent or mitigate injury caused by various threat agents, is commonly based on evidence of efficacy obtained in animals. Animal studies are necessary when human studies are not feasible and challenge studies are not ethical. The successful development of countermeasures to radio-nuclear threats that cause Acute Radiation Syndrome (ARS) provides the opportunity to explore potential areas of overlap in the scientific approaches to studies of injuries caused by radiation and sulfur mustard exposures in animals. The aim is to evaluate the available scientific knowledge for radiation threat agents and sulfur mustard for potential analogies of fundamental mechanisms of organ injury and dysfunction. This evaluation is needed to determine the applicability of regulatory strategies for product development and approval adopted by manufacturers of countermeasures for radiation threat agents. Key elements of an efficient development plan based on animal efficacy studies include characterizing the pathophysiology of organ injury and the mechanism of action (MOA) of the countermeasure; modeling the clinical condition in animals to establish the manifestations of the injury caused by various levels of exposures to the threat agent and the response to various doses of the countermeasure candidate; as well as selecting a maximally effective human dose.

Introduction

Libero Marzella, from the FDA's Division of Imaging and Radiation Medicine, in the Center for Drug Evaluation and Research (CDER) spoke on the development of drug products,[a] for the treatment of ARS. ARS is the term applied to a variety of clinical manifestations resulting from the exposure of humans to high doses of penetrating radiation in a very short period of time.

The aim of this regulatory talk was to emphasize key elements of drug development programs for products approved for the treatment of the hematopoietic subsyndrome of acute radiation syndrome (H-ARS) based on efficacy studies carried out under the Animal Rule.[b] Active product development is underway in another ARS subsyndrome, namely gastrointestinal ARS (GI-ARS) and in 2 additional organs affected by radiation, albeit with delayed manifestations of the injury, namely radiation-induced lung injury (RILI),[1] and cutaneous radiation injury (CRI).[2]

Drugs for ARS are developed under the Animal Rule because human challenge studies are not ethical and field trials are not feasible. In addition, the demonstration of drug effectiveness in a related condition of use (e.g., in myelosuppression induced by cancer therapies or in immune-mediated cytopenia) generally cannot be fully extrapolated to ARS because these conditions do not adequately reflect the ARS pathophysiology.

There are ongoing scientific discussions between the investigators working on animal models to develop consensus on various aspects of radiation injury including: pathophysiology; animal models and natural history of disease studies; organ-specific and systemic pharmacologic targets; interactions between radiation-affected organs; conditions that are the result of a downstream effect of the acute sequelae of exposure to ionizing radiation (e.g., sepsis secondary to radiation injury to the GI tract); concomitant therapies and supportive veterinary care; and efficacy outcomes and pharmacodynamic outcomes for the selection of an effective human dose. This cross-talk is important for the efficient development of medical countermeasures for radiation injury. The workshop provided the opportunity to explore various areas of overlap in the scientific approaches to investigations of injury caused by radiation and sulfur mustard exposures.

[a]As used in this article, the terms *drugs* or *drug products* refer to human drugs and biological products regulated by CDER; in addition, the term *approval* refers to approval or licensure.

[b]The term "Animal Rule" refers to the regulations that provide a pathway for approval of drug or biological products when human efficacy studies are not ethical or feasible. See 21 CFR 314.600 through 314.650 for drugs or 21 CFR 601.90 through 601.95 for biological products.

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Points to Consider

Investigators are encouraged to review the regulatory history of products approved for H-ARS and consider scientific literature reports of studies of products under development for treatment of skin and lung radiation injury. The aim is to evaluate the available scientific knowledge for radiation threat agents based on potential analogies of fundamental mechanisms of organ injury and dysfunction caused by radiation and sulfur mustard. This evaluation is needed to determine the applicability of regulatory strategies for product development and approval adopted by developers of countermeasures for radiation threat agents.

Sponsors typically request a pre-IND meeting with the FDA review division when they have information on chemistry, manufacturing, and controls (CMC); the mechanism of action of the investigational drug; the proposed indication for use; nonclinical proof-of-concept data or clinical data from a related indication that provide support for the activity of the drug; and an overall strategy for nonclinical and clinical development. Pre-IND meetings with the review division are particularly important for product development under the Animal Rule. These meetings are useful to prevent unnecessary studies, to increase the likelihood that needed studies will provide useful information, and to allow a discussion of scientific ideas and exchange of information and experience.

Selection of Pharmacologic Target

With regard to the selection of the pharmacologic target of the investigational drug, characterization of the pathophysiology of organ injury and dysfunction, as well as the MOA of the countermeasure are key for animal efficacy studies. The MOA of current therapies for H-ARS, namely the mitigation of myelosuppression manifesting with acute depletion of myeloid precursors, is well defined. Currently approved countermeasures stimulate proliferation, differentiation, and function of myeloid precursor cells. On the other hand, the pathophysiology of skin and lung radiation injury is less completely understood and more complex due to the potential for multiple organ dysfunction and a multistage clinical course with early acute edema and inflammation, delayed development of necrosis, and followed by repair/fibrosis. Hence the need for more complex studies with ongoing exploration of various pharmacologic targets.

Modeling the Clinical Condition in Animals

The initial phase of product development is generally accomplished through natural history of disease studies. These studies are necessary to establish the time course, manifestations of the injury caused by various levels of exposures to the threat agent, and the response to various doses of the countermeasure candidate. FDA has relied on adequate and well controlled efficacy studies in non-human primate models for the approval of H-ARS indications. Rodent studies have provided key supportive efficacy data. Supportive care including analgesia, hydration, nutrition, and antimicrobials is provided to all study arms.

Rhesus macaque is a commonly used non-human primate model for H-ARS and is under development for lung injury. Standardization of the animal model and minimization of variables are essential for reproducibility of outcomes. Currently, the limited availability of Rhesus macaques (attributable to the COVID-19 pandemic) is ensuring the validation of a cynomolgus macaque model. Generally, acute, systemic (rather than focal) irradiation is considered more representative of the clinical condition. Porcine animal models are under development for radiation-induced skin injury because of similarity of skin structure and function, and repair responses.

Developing Evidence of Effectiveness

For each of the drugs approved for H-ARS to date (i.e., leukocyte growth factors: filgrastim, pegfilgrastim, and sargramostim; and thrombopoietin receptor agonist: romiplostim), a single animal efficacy study in a single non-human primate model of H-ARS was required to provide substantial evidence of effectiveness, estimate the treatment effect, and help establish a dose and regimen for humans. The adequate and well-controlled animal efficacy studies demonstrated an increase in survival at a prespecified time point post-treatment (the prospectively defined primary endpoint) accompanied by the supportive evidence of the expected pharmacological effect (i.e., resolution of neutropenia or thrombocytopenia); therefore, the studies were relied on for approval. For each of the drugs discussed, the results of the adequate and well-controlled efficacy study were supported by existing human efficacy data from relevant approved indications.

Generally, conduct of studies in patients with organ injury and dysfunction caused by similar etiologic agents (e.g., chemotherapy) is encouraged to obtain clinical safety data, and when possible, supportive clinical efficacy data. Survival has been the primary animal efficacy endpoint for H-ARS and is under consideration for radiation-induced lung injury; the utility of quantitative measures of lung function or anatomy is under evaluation in these animal models.

For skin radiation injury, the quantitative assessment of area and depth of skin injury and repair verified by histopathology is recommended as the primary animal efficacy endpoint. Clinical utility could be demonstrated by a meaningful reduction in severe skin injury or improvement in healing; improvement in quality and durability of repair; as well as bridging to engraftment or reconstruction. Survival should be considered for safety assessments e.g., in models of combined injury.

Endpoints that characterize the recovery of organ injury or dysfunction (e.g., neutrophil or platelet counts that document recovery from myelosuppression, positive microbial cultures) have been considered secondary to survival and have been used to: support primary efficacy endpoints; trigger the initiation of supportive animal care; and pharmacodynamic modeling for selection of human dose.

Selection of Effective Human Dose

Dose-ranging studies of the investigational drug in animal models are necessary for the determination of the fully effective human dose. There are 2 approaches to the selection of human dose. The pharmacokinetic approach is based on the comparison of predicted drug exposure in affected humans to the exposure in animals receiving a fully effective dose, while the pharmacodynamic approach is based on the determination of the drug exposure in humans that results in a similar magnitude of the relevant PD marker achieved in animal models.

Conclusion

This article summarizes the key elements of successful regulatory strategies for the development of drug products for acute radiation syndrome under the Animal Rule. Studies of drugs approved for

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use in H-ARS and ongoing studies of drugs intended for use in radiation-induced skin and lung injury might be informative for the development of products for sulfur mustard induced injury. Investigators are encouraged to consult publicly available FDA drug approval packages and study reports in the scientific literature.

Competing interests. The author declares no competing interests.

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