Acute Radiation Syndrome: Developing Drugs for Prevention and Treatment

Guidance for Industry

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

April 2023
Animal Rule

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Acute Radiation Syndrome: Developing Drugs for Prevention and Treatment Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance provides information and recommendations to assist sponsors and other interested parties in the development of drugs[2] to prevent or treat acute radiation syndrome (ARS) caused by exposure to ionizing radiation from accidental or deliberate events. Generally, drugs developed for such indications will require approval under the regulations commonly referred to as the Animal Rule.[3]

This guidance is not intended to address the development of drugs to prevent or treat conditions that are the result of a downstream effect of the acute sequelae of exposure to ionizing radiation or secondary conditions in the setting of ARS (e.g., sepsis secondary to radiation injury to the gastrointestinal (GI) tract). Furthermore, this guidance does not address delayed effects of acute radiation exposure (e.g., radiation-induced lung injury) or decorporation agents.[4]
The general principles expressed in this guidance are based on the guidance for industry *Product Development Under the Animal Rule* (October 2015) (hereafter referred to as the Animal Rule

[1] This guidance has been prepared by the Divisions of Imaging and Radiation Medicine and Pharmacology-Toxicology in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

[2] As used in this guidance, the terms *drugs* or *drug products* refer to human drugs and therapeutic biological products regulated by CDER, unless otherwise specified. In addition, the term *approval* refers to approval or licensure, unless otherwise specified.

[3] The Animal Rule provides 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). Additional information about the Animal Rule is available at https://www.fda.gov/emergency-preparedness-and-response/mcm-regulatory-science/animal-rule-information.

[4] For information on decorporation agents, see the guidance for industry *Internal Radioactive Contamination — Development of Decorporation Agents* (March 2006). We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

guidance). Developing products under the Animal Rule can be very challenging. Establishing early and ongoing communication with the review division is critical for a successful outcome.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

ARS is the term applied to a variety of clinical manifestations resulting from the exposure of humans to high doses of radiation. The Centers for Disease Control and Prevention (CDC) defines ARS as "an acute illness caused by irradiation of the entire body (or most of the body) by a high dose of penetrating radiation in a very short period of time (usually a matter of minutes)."[5] CDC further describes three classic ARS subsyndromes as hematopoietic syndrome (H-ARS), gastrointestinal syndrome (GI-ARS), and cardiovascular/central nervous system syndrome. ARS usually will be accompanied by some skin damage. The predominance of expression of these clinical subsyndromes is highly dependent on the magnitude and extent of radiation exposure and the time following exposure.

III. DEVELOPMENT PROGRAM

A. Overview of Drug Development

For a drug product to be approved by FDA, a sponsor must provide substantial evidence[6,7] that the drug has the effect it purports to have under the conditions of use described in the proposed labeling and that the drug's benefits outweigh its risks. Generally, the evidence is derived from adequate and well-controlled clinical studies. Human challenge studies (i.e., exposing volunteers to acute, high doses of ionizing radiation to study the effects of the drug) are not ethical and field trials are not feasible when developing drugs for ARS. Under such circumstances, FDA may grant approval under the Animal Rule, based on adequate and well-controlled animal efficacy studies, when the results of those studies establish that the drug is reasonably likely to produce clinical benefit in humans. However, it is important to note that under the Animal Rule, human studies are still required to demonstrate a drug's safety.[8]

[5] See Acute Radiation Syndrome: A Fact Sheet for Clinicians, available at https://www.cdc.gov/nceh/radiation/emergencies/arsphysicianfactsheet.htm.

[6] The FD&C Act section 505(d) (21 U.S.C. 355(d)).

[7] The Public Health Service Act section 351 (42 U.S.C. 262).

[8] 21 CFR 314.600 and 314.610(a) for drugs and 21 CFR 601.90 and 601.91(a) for biological products.

In some circumstances, efficacy studies conducted in humans with the investigational drug for conditions with pathophysiology similar to that of ARS may provide confirmatory evidence for approval. For leukocyte growth factor (LGF) and thrombopoietin receptor agonist drugs approved for use in H-ARS, examples of confirmatory evidence include efficacy studies in subjects with cancer receiving myelosuppressive chemotherapy or myeloablative regimens before bone marrow transplantation and studies in subjects with immune thrombocytopenia who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy.

Improving capabilities for addressing radiological and nuclear emergencies is a national priority.[9] FDA has developed distinct approaches to facilitate and expedite development and review of new drugs to address unmet medical needs for treating serious or life-threatening conditions.[10] Drugs developed for ARS may be eligible for certain FDA expedited programs (e.g., fast track and priority review) or other FDA programs (e.g., orphan drug designation).[11] Sponsors requesting these designations should use established procedures.[12] Breakthrough therapy designation requires preliminary clinical evidence demonstrating that the drug may have substantial improvement on at least one clinically significant endpoint over available therapy.[13,] Drugs being developed under the Animal Rule might meet the statutory requirement for breakthrough therapy designation when there is such preliminary clinical evidence in a condition closely related to the indication sought under the Animal Rule. For example, clinical evidence in chemotherapy-induced myelosuppression might support breakthrough therapy designation for ARS-associated myelosuppression.

Developing the animal models in which to test the efficacy of investigational products being developed under the Animal Rule is challenging. Animal models should reflect the clinical condition for which the drug is being developed (e.g., H-ARS or GI-ARS). The Animal Rule guidance defines animal model as "a specific combination of an animal species, challenge agent, and route of exposure that produces a disease process or pathological condition that in multiple important aspects corresponds to the human disease or condition of interest."[14] Given the multisystem nature of ARS, radiation exposure directed at sections of the body (e.g., thoracic or abdominal region) may be of limited value for confirmatory studies. Therefore, total-body

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[9] See Radiological and Nuclear Emergency Preparedness Information from FDA, available at https://www.fda.gov/emergency-preparedness-and-response/mcm-issues/radiological-and-nuclear-emergency-preparedness-information-fda.

[10] See the guidance for industry *Expedited Programs for Serious Conditions – Drugs and Biologics* (May 2014).

[11] Information on orphan drug designation is available at https://www.fda.gov/industry/medical-products-rare-diseases-and-conditions/designating-orphan-product-drugs-and-biological-products.

[12] See Appendix 1, Processes for Fast Track, Breakthrough Therapy, and Priority Review Designations, in the guidance for industry *Expedited Programs for Serious Conditions – Drugs and Biologics*.

[13] See section 506 of the FD&C Act (21 U.S.C. 356) (as amended by the Food and Drug Administration Safety and Innovation Act, Public Law 112-144). See also section VI. A, Qualifying Criteria for Breakthrough Therapy Designation, in the guidance for industry *Expedited Programs for Serious Conditions – Drugs and Biologics.*

[14] See the guidance for industry *Product Development Under the Animal Rule* (October 2015).

irradiation with or without partial bone marrow sparing (e.g., 2.5 percent or 5 percent) is recommended in the animal studies. Sponsors should conduct the efficacy studies in a manner consistent with the ethical use of animals and use the minimum number of animals necessary to ensure scientifically valid results.[15]

Sponsors should consider factors such as age and sex, which may contribute to differences in the responses to drugs being developed under the Animal Rule to treat or prevent ARS. Sponsors should discuss with the review division how they intend to address the effects of demographic factors such as age and sex on the susceptibility to radiation and the response of their investigational drug in animal models. In general, efficacy studies in juvenile animals are not required because efficacy can be extrapolated from adult animals and pharmacokinetic/pharmacodynamic (PK/PD) data to determine dosing in pediatric patients. Sponsors are required to submit an initial pediatric study plan[16] to their investigational new drug application (IND) no later than 60 calendar days after the date of the end-of-phase 2 meeting unless the drug has been granted orphan designation for the proposed ARS indication.[17] Sex-specific differences in the susceptibility to radiation-induced injury occur in animal models of ARS resulting in differences in mortality and in physiological responses to radiation. However, sex-specific differences in response to approved treatments have not been identified. It is important to determine whether sex-based differences in animal models of ARS are associated with differential response to an investigational treatment.

The Agency encourages sponsors to establish early and ongoing communication to develop a drug development plan that will support the proposed indication (e.g., anticipated clinical use, dosing regimen, and route of administration). The approved ARS indication will generally include the subsyndrome or organ system that is affected by the radiation and mitigated by the therapy and the nature of the benefit observed in the animal efficacy studies, typically increased survival or prevention of major morbidity. The mechanism of action of the drug must be reasonably well-understood for approval under the Animal Rule[18] and must be described in the product labeling.[19] For example, certain hematopoietic growth factor or thrombopoietin receptor agonist products stimulate the proliferation and differentiation of progenitor cells in the bone marrow and increase recovery of progenitor cells and survival of animals after myelosuppressive doses of radiation. Growth factors targeting different progenitor cells in other organs might

[15] Approval under the Animal Rule requires adequate and well-controlled animal efficacy studies; however, we support the principles of the 3Rs, to reduce, refine, and replace animal use in testing when feasible. We encourage sponsors to consult with FDA if they wish to use a nonanimal testing method they believe is suitable, adequate, validated, and feasible. We will consider if such an alternative method could be assessed for equivalency to an animal test method. See also https://www.fda.gov/science-research/about-science-research-fda/advancing-alternative-methods-fda.

[16] See section 505B(e)(2) of the FD&C Act (21 U.S.C. 355c).

[17] See section 505B(k)(1) of the FD&C Act (21 U.S.C. 355c). See also the guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Initial Pediatric Study Plans* (July 2020).

[18] 21 CFR 314.610(a) for drugs and 21 CFR 601.91(a) for biological products.

[19] 21 CFR 201.57(c)(13)(i)(A).

increase survival by, for example, promoting recovery of gastrointestinal mucosa in GI-ARS. A broad indication for increase in survival agnostic of organ system may be based upon evidence of improved survival attributable to any one of several mechanisms of drug action, such as enhancing the recovery of the multiorgan injury of ARS (e.g., modulators of immune responses or of programmed cell death).

Design considerations for animal efficacy studies would be different for a drug for prophylaxis compared with a drug for treatment. Pre-exposure prophylaxis studies should be designed to determine the likely time course of the prophylactic effect (i.e., the minimum time the subject must wait after taking the drug before radiation exposure) and how long the prophylactic effect lasts. Study design should also incorporate standard of care for postradiation exposure treatment, including the potential concurrent use of LGFs, for example.

A product being developed for ARS may be considered for use under an emergency use authorization or under an expanded access mechanism. An emergency use authorization is a regulatory mechanism by which, under certain emergency circumstances and when a requisite declaration under section 564(b) of the FD&C Act is in place, the FDA Commissioner may authorize the use of unapproved medical products or the unapproved use of approved medical products to diagnose, treat, or prevent serious or life-threatening diseases or conditions caused by a chemical, biological, radiological, or nuclear threat agent that is the subject of such declaration, when, among other criteria, there are no adequate, approved, and available alternatives.[20] Expanded access is a potential pathway for a patient with an immediately life-threatening condition or serious disease or condition to gain access to an investigational drug product for treatment outside of clinical trials when no comparable or satisfactory alternative therapy options are available.[21]

B. Early Drug Development

Sponsors typically request a pre-IND meeting with the review division when they have information on chemistry, manufacturing, and controls (CMC), the mechanism of action, proposed use, nonclinical proof-of-concept or clinical data from a related indication that provides support for the mechanism of action, and an overall strategy for nonclinical and clinical development of the investigational drug. Sponsors may request a pre-IND meeting at earlier stages of product development if needed. The appropriateness of the proposed animal models is an important topic for discussion at this meeting. Efficacy studies in nonhuman primates (NHPs) are not required to support either a pre-IND meeting request or the filing of an IND. Exploratory efficacy studies may be conducted in any acceptable (e.g., agreed-upon, pharmacologically relevant) species.

[20] For more information on emergency use authorizations, please see the guidance for industry and other stakeholders *Emergency Use Authorization of Medical Products and Related Authorities* (January 2017).

[21] For more information on expanded access mechanisms, see https://www.fda.gov/news-events/expanded-access/expanded-access-information-industry.

Pre-IND meetings with the review division are particularly important for product development under the Animal Rule. Pre-IND 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.[22] The review division will work with sponsors to clarify their best path forward, including the most appropriate animal models, primary endpoints for efficacy studies, and PD endpoints to support dose translation. FDA recognizes that, in some instances, a series of meetings[23] (such as Type C meetings) rather than only a single meeting might be required in the pre-IND stage.

1. Selection of Doses for Development

For selection of a human dose based on a PD marker, the PD marker should be shown in animals and humans to correlate with the mechanism of action by which the drug prevents or substantially reduces the radiation-induced condition and with the desired clinical outcome (i.e., enhancement of survival or prevention of major morbidity). In addition, human PK/PD studies should support a human drug dose that would result in PD marker levels in the desired range that is predictive of marker levels associated with efficacy in the adequate and well-controlled animal studies. The PD marker and its assay methods and performance characteristics in the animal species and in humans should be described and agreed upon with FDA.

In the absence of an accepted PD marker, an approach for dose selection for systemically absorbed drugs should be based on a comparison of relevant exposure parameters in the animal species and humans.[24]

2. Drug Development Plan

The following is a potential sequence for conducting animal and human studies to support a marketing application for an ARS drug under the Animal Rule:

- Preclinical evaluation of drug pharmacology (e.g., potency against target, selectivity) and toxicity.

- Natural history studies to characterize and select animal models that are intended to be translational or candidate models as adequate and well-controlled studies under the Animal Rule. Selected animal models should adequately reflect the radiation-induced injury in humans, including the time course and manifestations of the injury. In addition,

[22] Pre-IND/IND information is available at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/default.htm.

[23] See the draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products* (2017). When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[24] For a detailed discussion, see section V. B, Elements Related to the Investigational Drug and the Selection of an Effective Dose in Humans, in the Animal Rule guidance.

the pharmacology of the drug (e.g., the pathophysiological role and tissue distribution of the molecular target of the drug) should be generally similar in the animal models and in humans.

- Exploratory animal efficacy studies conducted in relevant animal models.

- PK studies, conducted in relevant animal models, ideally employing a range of drug doses to support selection of the human dose and regimen.

- Animal safety pharmacology and toxicology studies.

- Single dose (and multiple doses, if needed), dose-escalation, safety, and PK studies in healthy humans using doses that are appropriately safe based upon toxicology studies and have appropriate PD activity based upon exploratory animal studies.

- Adequate and well-controlled animal efficacy studies conducted in the agreed-upon animal models as well as PK and/or PD studies in those species necessary to support the human dose selection (e.g., dose-finding studies necessary for understanding the exposure/response relationship in the proposed animal models).

- Additional human safety studies to provide an adequate safety database (see section F).

Under the Animal Rule, the nonclinical studies needed to support human safety trials are the same as those required under traditional drug development with the expectation that nonclinical safety and toxicity studies generally should be conducted under good laboratory practice (GLP) regulations (21 CFR part 58).[25]

There are no regulations that specifically address data quality and integrity issues for the adequate and well-controlled animal efficacy studies and the PK and/or PD studies in animals used to select a dose and regimen for humans (i.e., dose conversion studies); however, FDA recommends following GLP regulations to the extent practicable. The Agency recognizes the technical and practical challenges in conducting studies in irradiated animals, and there may be justifiable limitations in the ability to apply the GLP regulations when conducting these studies.

Before initiating these studies, sponsors should identify aspects of the studies anticipated to be a challenge regarding the GLP regulations and propose methods for adapting the studies to ensure the quality and integrity of the resulting data. Sponsors should seek concurrence from the review division on the data quality and integrity plan before initiating studies.[26] There may be other nonclinical studies for which the review division may recommend using GLP regulations, to the

[25] For further information about these nonclinical studies, see the ICH guidances for industry *M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals* (January 2010) and *S6(R1) Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals* (May 2012).

[26] For a detailed discussion, see section IV. B, Study Conduct, in the Animal Rule guidance.

extent practicable. If there is any question about whether any nonclinical study should be conducted under GLP, sponsors should consult the review division.

C. CMC

A sufficiently characterized drug is critical to relate the drug used in Animal Rule–specific nonclinical studies to the drug proposed for use in human studies. Sponsors should perform the adequate and well-controlled animal efficacy studies intended to support approval and human safety studies using the to-be-marketed drug formulation. Any differences between the formulation used and the to-be-marketed formulation should be discussed with the review division before studies are initiated. If the animal model used makes dosing with the to-be-marketed human drug formulation difficult, sponsors should administer the drug to the animals using a dosing regimen that would provide drug exposures comparable to those in humans.

Sufficient CMC characterization is necessary for the adequate and well-controlled animal efficacy studies that provide the primary evidence of effectiveness for approval under the Animal Rule and for the PK and/or PD studies that are used to select the drug dose and regimen in humans.[27]

Drugs, as defined under section 201(g) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), contain active ingredients and may contain inactive ingredients. As such, study drug ingredients are required to be produced at facilities that comply with current good manufacturing practice (CGMP) requirements under section 501(a)(2)(B) of the FD&C Act.[28] When an IND is submitted, regulations under 21 CFR 312.23(a)(7) require including the CMC section in the IND describing the composition, manufacture, and control of the drug substance and the drug product. This information is necessary to ensure the proper identification, quality, purity, and strength of the investigational drug. The amount of information needed to make that assurance will vary with the phase of the investigation, the proposed formulation, and duration of the investigation.[29]

For the preparation of the CMC section of an IND, refer to the guidance for industry *Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-derived Products* (November 1995), which contains guidance on the format and the content of the CMC section of the IND. For recommendations regarding CMC requirements at the stage of the adequate and well-controlled animal efficacy studies, refer to the guidance for industry *INDs for Phase 2 and Phase 3 Studies Chemistry, Manufacturing, and Controls Information* (May 2003).

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[27] 21 CFR 312.23(a)(7).

[28] According to the guidance for industry *Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients* (September 2016), CGMP controls should be implemented after the designation of starting materials.

[29] 21 CFR 312.23(a)(7). For CMC information included in IND applications, please see also the following FDA website: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/ucm362283.htm.

The approach to producing investigational drugs in compliance with CGMP requirements may vary based on the phase of the clinical trial. The FDA guidance for industry *CGMP for Phase 1 Investigational Drugs* (July 2008) provides more information on this topic. Investigational drugs must comply with the statutory requirements for CGMP under section 501(a)(2)(B) of the FD&C Act.

D. Establishing Efficacy in Animals

Studies should be conducted to establish a lethality profile and define the radiation dose-response relationship in the selected species (and strain or substrain when relevant) and include periods of observation appropriate for the ARS subsyndrome and species. The dose-response curve generated should be compared with curves from studies of similar design reported in the scientific literature. Sponsors should explain any important differences. FDA recommends that each testing facility confirm the reproducibility of its dose-response curves periodically and as necessary (e.g., if there are major changes in standard operating procedures).

Various radiation sources and types may be used in nonclinical studies. The metric of biological effect (e.g., $LD_{50/60}$, or lethal dose sufficient to kill 50 percent of irradiated animals within 60 days) can be attained through controlled irradiation conditions irrespective of radiation source or radiation type. Sponsors should provide a detailed justification for the source and type of radiation, the dose or doses to be used in a study, how the animals would be irradiated, and the relevance to the intended clinical conditions of use. A determination of dose modification factor (i.e., a demonstration that the mortality caused by various radiation doses in treated animals can be matched at any level of radiation by a constant fraction of the radiation dose in untreated animals) is not required. For the adequate and well-controlled animal efficacy studies, FDA generally considers demonstration of efficacy against the effects of a single dose level of radiation to be sufficient (e.g., animals exposed to a single dose of 10 Gy); however, there may be circumstances for which FDA would recommend that a sponsor test its investigational drug against the effects of a range of dose levels of radiation (e.g., animals exposed to a single dose of 7.0, 8.5, or 10 Gy).

The Agency recommends that sponsors standardize and document the time of day that each animal is irradiated given the potential impact of circadian rhythms on responses to irradiation.[30,31]

Regarding the number of animal species studied to demonstrate a drug's treatment effect, the Animal Rule requires that "the effect is demonstrated 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

[30] Williams, JP, SL Brown, GE Georges, M Hauer-Jensen, RP Hill, AK Huser, DG Kirsch, TJ MacVittie, KA Mason, MM Medhora, JE Moulder, P Okunieff, MF Otterson, ME Robbins, JB Smathers, and WH McBride, 2010, Animal Models for Medical Countermeasures to Radiation Exposure, Radiat Res, 173(4):557–578.

[31] Plett, PA, CH Sampson, HL Chua, M Joshi, C Booth, A Gough, CS Johnson, BP Katz, AM Farese, J Parker, TJ MacVittie, and CM Orschell, 2012, Establishing a Murine Model of the Hematopoietic Syndrome of the Acute Radiation Syndrome, Health Phys, 103(4):343–355.

response in humans."[32] Decisions about the adequacy of a single model are made by the Agency on a case-by-case basis after considering all available data to determine how well the single-animal model represents the clinical condition and how translational the model is expected to be. Factors to be considered in determining the adequacy of the animal model or models include the ARS manifestations and time course in animals versus humans, the similarities and differences in the pathophysiology of the radiation-induced condition between animals and humans, the pharmacology of the target of the investigational drug in animal species relative to humans, and the PD/efficacy relationship in animals relative to the PD response in humans. Confirmatory evidence of efficacy might be derived from data in a somewhat similar human condition.

The Animal Rule states: "In assessing the sufficiency of animal data, the agency may take into account other data, including human data, available to the agency."[33] For example, the Agency determined that efficacy demonstrated in the rhesus macaque model used for the H-ARS indication for filgrastim and other LGFs is acceptable because of the available human efficacy data in patients with myelosuppression or myeloablation attributable to cancer therapy or accidental radiation exposure who were treated with LGFs.

When a drug is pharmacologically active only in humans and is intended to address an unmet medical need for ARS, the use of a surrogate drug that achieves the engagement of the pharmacological target in animals may be considered for the animal efficacy studies. In such circumstances, it is strongly recommended that sponsors meet with the review division to determine the adequacy of a surrogate drug for the adequate and well-controlled efficacy studies.

It is important to ensure the humane care and use of the laboratory animals to minimize distress and pain and to provide nutritional and fluid support. Supportive care, as defined in the Animal Rule guidance, "is needed only to mimic, to the extent possible, the human clinical scenario." If the expected clinical scenario is to use the drug in a mass-casualty situation in which supportive care is not immediately available, the adequate and well-controlled animal efficacy studies necessary for approval may be conducted with adequate veterinary care necessary to minimize pain and suffering. Alternatively, if the expected clinical setting is to use the drug in a situation in which supportive care is available, FDA recommends that sponsors propose and justify a supportive care regimen that will mimic the proposed use of the product. Sponsors should discuss all animal care interventions with the review division.[34]

E. Efficacy Endpoints

Generally, 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 effectiveness of a drug in a related condition of use (e.g., in myelosuppression induced by cancer therapies or in

[32] 21 CFR 314.610(a)(2) for drugs and 21 CFR 601.91(a)(2) for biological products.

[33] 21 CFR 314.610(a) for drugs and 21 CFR 601.91(a) for biological products.

[34] See Section IV. C. and Appendix B in the Animal Rule guidance.

immune-mediated cytopenia) generally cannot be fully extrapolated to ARS because these conditions do not adequately reflect the ARS pathophysiology.

For each of the drugs approved for H-ARS to date (i.e., LGFs: filgrastim, pegfilgrastim, and sargramostim; and thrombopoietin receptor agonist: romiplostim), a single animal efficacy study in a single NHP model of H-ARS was required to provide substantial evidence of effectiveness, estimate the treatment effect, and 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 posttreatment (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, enhancing survival or preventing major morbidity should be the primary endpoint in animal efficacy studies.[35] In addition to improved survival, endpoints reflecting reduction in important ARS complications or prevention of major morbidity, such as fewer major hemorrhages, needed transfusions, or serious infections, may also be acceptable as primary efficacy outcomes. For a survival benefit, overall survival at a relevant time point (e.g., when the proportion of animals surviving has plateaued), rather than only reduction in time to death without any difference in the proportion of animals that ultimately survive, should be demonstrated. The timing of assessing the primary endpoint should be based upon natural history studies. Typically, survival should be evaluated for 30 days for rodents and 60 days for nonrodents, given that their Kaplan-Meier survival curves after radiation exposure plateau at these time points in these animals. PD endpoints, such as a favorable effect on neutropenia in an efficacy study of an LGF, are useful in supporting the mechanism of action of the drug and for selecting an effective dose and regimen in humans and are considered secondary efficacy endpoints. Sponsors are strongly encouraged to discuss potential efficacy endpoints in animal studies with the review division before starting the study.

GI-ARS generally occurs after exposure to a much greater radiation dose than H-ARS (e.g., $LD_{50/15}$ of 11.33 Gy for GI-ARS versus $LD_{50/60}$ of 7.54 Gy for H-ARS in NHP total-body irradiation models).[36] Therefore, even when GI-ARS is the intended target for therapy, the animal models and the efficacy outcomes should consider the manifestations of H-ARS. For example, improvement in survival at 10 to 15 days in an animal model of GI-ARS will provide useful information on a drug's activity in exploratory, proof-of-concept studies before lethality attributable to H-ARS ensues. To provide substantial evidence of effectiveness of an investigational drug for the treatment of GI-ARS, it is important to study the effect of the drug on overall survival and safety assessed at a time point defined by natural history studies of radiation doses that induce GI-ARS (e.g., 30 and 60 days, respectively, in rodents and NHPs). For this objective, a clinically relevant animal model might consist of a total-body irradiation model with

[35] See 21 CFR 314.610(a)(3) for drugs and 21 CFR 601.91(a)(3) for biological products.

[36] Farese, AM, AW Bennett, AM Gibbs, KG Hankey, K Prado, W Jackson, III, and TJ MacVittie, 2019, Efficacy of Neulasta or Neupogen on H- and GI-ARS Mortality and Hematopoietic Recovery in Nonhuman Primates After 10 Gy Irradiation With 2.5% Bone Marrow Sparing. Health Phys, 116(3):339–353.

partial bone marrow sparing and supportive therapy that permit recovery from H-ARS as well as evaluation of the investigational drug efficacy based on survival from GI-ARS injury. Acceptable secondary efficacy endpoints may include assessment of GI function (e.g., malabsorption, body weight loss, mucosal barrier function, diarrhea, dehydration, vomiting) and structure (e.g., histopathologic assessment of viable crypts, apoptotic cells, and villus height).

F. Clinical Safety Studies

Certain investigational drugs under development for treating ARS might be associated with severe adverse reactions that preclude a full characterization of the drug's safety in healthy adult volunteers. The Agency will not rely primarily on nonclinical information to assess safety; approval of a new drug requires an adequate human safety database, regardless of the regulatory development pathway.[37,38] If nonclinical or clinical data raise safety concerns about further testing of the investigational drug in healthy adult volunteers, sponsors should consider acquiring the needed human safety information in a patient population for which the drug offers a potential benefit that justifies the drug's risks. Human safety data from a drug development program for which the drug's benefit-risk is appropriate could then be used to support the ARS indication. Sponsors should provide a justification for extrapolating to ARS the human safety data from the clinical condition chosen.

Because approval of drugs under the Animal Rule also requires an adequate human safety database, clinical safety data from previous clinical experience may be applicable. For example, the safety of certain LGFs for use in H-ARS was extrapolated from the previously approved clinical uses in oncology indications.

G. Requirement for Postmarketing Evaluation

The Animal Rule requires sponsors to conduct postmarketing studies to verify the drug's clinical benefit and to assess its safety when such studies are feasible and ethical and to include with the marketing application a plan or approach to conducting such a study.[39] FDA recommends that an ARS study protocol be developed to specify collection of data (as feasible) for exploring covariates affecting survival such as age, estimated absorbed dose of radiation, ARS drug treatment, treatment dose, duration, and time to initiation of treatment after radiation exposure.

[37] 21 CFR 314.600 and 314.610(a) for drugs and 21 CFR 601.90 and 601.91(a) for biological products.

[38] See also 67 FR 37988 at 37989 (May 31, 2002).

[39] 21 CFR 314.610(b)(1) for drugs and 21 CFR 601.91(b)(1) for biological products.