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Authors: Satyamitra, Merriline M., Perez-Horta, Zulmarie, DiCarlo, Andrea L., Cassatt, David R., Rios, Carmen I., et al.

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MEETING REPORT

NIH Policies and Regulatory Pathways to U.S. FDA licensure: Strategies to Inform Advancement of Radiation Medical Countermeasures and Biodosimetry Devices

Merriline M. Satyamitra,[a,1] Zulmarie Perez-Horta,[a] Andrea L. DiCarlo,[a] David R. Cassatt,[a] Carmen I. Rios,[a] Paul W. Price[b] and Lanyn P. Taliaferro[a]

[a] *Radiation and Nuclear Countermeasures Program (RNCP), and* [b] *Office of Regulatory Affairs, Division of Allergy, Immunology, and Transplantation (DAIT), National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH), United States Department of Health and Human Services (HHS), Rockville, Maryland 20892-9828*

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The Radiation and Nuclear Countermeasures Program within the National Institute of Allergy and Infectious Diseases (NIAID), is tasked with the mandate of identifying biodosimetry tests to assess exposure and medical countermeasures (MCMs) to mitigate/treat injuries to individuals exposed to significant doses of ionizing radiation from a radiological/nuclear incident, hosted. To fulfill this mandate, the Radiation and Nuclear Countermeasures Program (RNCP), hosted a workshop in 2018 workshop entitled "Policies and Regulatory Pathways to U.S. FDA licensure: Radiation Countermeasures and Biodosimetry Devices." The purpose of the meeting was to facilitate the advancement of MCMs and biodosimetry devices by assessing the research devices and animal models used in preclinical studies; government policies on reproducibility, rigor and robustness; regulatory considerations for MCMs and biodosimetry devices; and lessons learned from sponsors of early stage MCM or biodosimetry devices. Meeting presentations were followed by a NIAID-led, open discussion among academic investigators, industry researchers and U.S. government representatives.

INTRODUCTION

The Radiation and Nuclear Countermeasures Program (RNCP), within the National Institute of Allergy and Infectious Diseases (NIAID), encourages communication between academic and industry researchers, as well as U.S. government (USG) agencies involved in the development and approval of radiation medical countermeasures (MCMs) and biodosimetry devices to assess and mitigate radiation injuries resulting from a radiological/nuclear mass casualty event. This has resulted in the approval of four radiation medical countermeasures: filgrastim (Neupogen®, FDA approved March 2015; Amgen, Thousand Oaks, CA),[2] pegfilgrastim (Neulasta®, FDA approved November 2015; Amgen),[3] sargramostim (Leukine®, FDA approved March 2018; Partner Therapeutics)[4] and romiplostim (Nplate®, FDA approved January 2021, Amgen).[5] However, to date, no device or test for radiation biodosimetry has been authorized, cleared, or approved by the FDA, and many acute and delayed syndromes after irradiation (e.g., gastrointestinal, cutaneous, cardiovascular, renal, pulmonary, etc.) require MCM approval. One of the biggest hindrance to successfully translate preclinical findings to the clinics lies in the lack of consistent and reproducible data (*1*), (discussed under session IV).

To this end, on October 9–10, 2018 in Bethesda, MD, the NIAID sponsored a workshop on ''Policies and Regulatory Pathways to FDA licensure: Radiation Countermeasures and Biodosimetry Devices.'' Speakers included academicians, industry and USG partners (Table 1). Objectives of this meeting were to:

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[1] Address for correspondence: Merriline M. Satyamitra, Ph.D., DAIT, NIAID, NIH, 5601 Fishers Lane, Rockville, MD 20852; email: merriline.satyamitra@nih.gov.

[2] https://bit.ly/2ZJO9KH.
[3] https://bit.ly/2U8OwdE.
[4] https://bit.ly/2XYai6h.
[5] https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/125268s167lbl.pdf.

TABLE 1
Workshop Speakers and Their Areas of Expertise

Name	Affiliation	Area of expertise
Brooke Buddemeier	Lawrence Livermore National Laboratory, Livermore, CA	Nuclear terrorism risk assessment, radiological response preparedness, modeling
John Koerner	ASPR, HHS, Washington DC	CONOPS, preparedness, emerging, threats, SNS
Karla Thrall	AltaScience, Everett, WA	Animal models of radiation, NHP, MCM testing
Lynne Wathen	BARDA, HHS, Washington DC	Radiation Biodosimetry, device clearance, bridging studies
Patricia Valdez	OD, NIH, Bethesda, MD	NIH policy, Rigor and Reproducibility
Francisca Reyes-Turcu	CDRH, FDA, White Oaks, MD	Device advanced development, Biodosimetry Guidance
Libero Marzella	CDER, FDA, White Oak, MD	Regulatory development of MCM, Animal Rule
David Cassatt	NIAID, NIH, Rockville, MD	Toxicology, product development, MCMs, immunology
Paul Price	NIAID, NIH, Rockville, MD	Regulatory affairs, drug discovery and development, devices
Rodney Wallace	BARDA, HHS, Washington DC	Radiation Biodosimetry Advancement, BARDA mission
Jacqueline Kline	Amgen, Washington DC	Regulatory affairs, biotechnology, MCM development
Michael Greenstein	SRI International, Menlo Park, CA	Medical device, lateral flow assay, IVD
List of USG panelists participating in the NIH-Guided discussion		

RNCP- The Radiation and Nuclear Countermeasures Program, NIAID
ORA- Office of Regulatory Affairs, NIAID
ASPR- The Office of the Assistant Secretary of Preparedness and Response
BARDA- The Biomedical Advanced Research and Development Authority
NCI-National Cancer Institute
DoD- Department of Defense
CTECS- Counter-Terrorism and Emergency Coordination Staff, FDA
CDER- Center for Drugs Evaluation and Research, FDA
CDRH- Center for Diagnostics and Radiological Health, FDA
HHS-Health and Human Services, CA-California, DC-District of Columbia, MD-Maryland

1. Capture current policies and regulatory pathways for efficient translation of products from basic research to advanced MCM and biodosimetry development,
2. Identify resources, guidance, and gaps in research practices and existing policies in the radiation product development space, and
3. Provide a platform for an open, informal dialogue among scientists with expertise in MCM or biodosimetry development, and representatives from USG funding and regulatory agencies tasked with advancing MCMs toward U.S. Food and Drug Administration (FDA) licensure.

Discussion topics centered on 1. defining the context for deployment of MCMs and biodosimetry platforms, 2. animal models of irradiation developed in response to FDA Animal Rule and Biodosimetry Guidance and a discussion of those policies, 3. how to pursue USG support for MCM development and biodosimetry advancement, and 4. lessons learned from industry frontrunners in MCM and biodosimetry development. This report summarizes the talks presented and participating panelist (Table 1), and main points brought forward during panel and participant discussions, but is not a comprehensive review of all models, MCMs in development, and all biodosimetry assays. The workshop concluded with the emphasis on producing reproducible data using well-characterized animal models, and the need for early and consistent interactions among subject matter experts, funding agencies, and the regulatory body for successful outcome in MCM and biodosimetry research.

SESSION I: Defining the Context for Deployment of MCMs and Biodosimetry Platforms

Response Needs after a Nuclear Detonation (B. Buddemeier)

The foundation of any response to a nuclear incident, and the policies that drive MCM and biodosimetry development rests on an understanding of the scenarios anticipated to be faced by the USG as well as state and local entities. Several USG agencies have produced computer models and planning documents (Table 2) based on explosion of a 10 kiloton (kT) nuclear device at ground level. Each model addresses the potential damage to structures and systems, and injuries and radiation exposures to people in the vicinity of the blast. These models take into account a number of sites, weather conditions, and time of day that would define the damage zone. Close to the detonation site, blast, burn, and damage from debris would predominate, while farther out, ionizing radiation would be the significant concern. Radionuclides adhering to debris particles would be carried by the prevailing winds and be deposited as fallout, with the decay of the radionuclides leading to potential human exposures (*2*).

These models have been refined to examine the effects of dense radionuclide buildup that occurs in an urban environment, which can affect radiation exposure to humans as well as the pattern of other damage. The models also consider how many individuals will need to be evaluated for injuries and radiation exposure and how many will need immediate or near-term medical attention. What kind of care to be administered will also be required, such as wound and

TABLE 2
Guidance for Medical Needs after a Nuclear Terrorism Incident

Title	Year published	Web site
Planning Guidance for Response to a Nuclear Detonation	2010	https://www.fema.gov/media-library-data/20130726-1821-25045-3023/planning_guidance_for_response_to_a_nuclear_detonation___2nd_edition_final.pdf
Reducing the Consequences of a Nuclear Detonation: Recent Research	2010	https://www.nae.edu/19920/Reducing-the-Consequences-of-a-Nuclear-Detonation-Recent-Research
Disaster Medicine and Public Health Preparedness (Volume 5 – Issue S1)	2011	https://www.cambridge.org/core/journals/disaster-medicine-and-public-health-preparedness/issue/88778038F4A65D3994DE59A8ABEDBB0A
NCRP Report No. 165, Responding to a Radiological or Nuclear Terrorism Incident: A Guide for Decision Makers	2011	https://ncrponline.org/publications/reports/ncrp-report-165/
Improvised Nuclear Device Response and Recovery: Communicating in the Immediate Aftermath	2013	https://www.fema.gov/sites/default/files/documents/fema_improvised-nuclear-device_communicating-aftermath_june-2013.pdf
Quick Reference Guide: Radiation Risk Information for Responders Following a Nuclear Detonation	2016	https://www.dhs.gov/sites/default/files/publications/Quick%20Reference%20Guide%20Final.pdf
Health and Safety Planning Guide for Protecting Responders Following a Nuclear Detonation	2016	https://www.dhs.gov/sites/default/files/publications/IND%20Health%20Safety%20Planners%20Guide%20Final.pdf
Nuclear/Radiological Incident Annex to the Response and Recovery Federal Interagency Operational Plans	2020	https://www.fema.gov/sites/default/files/2020-07/fema_incident-annex_nuclear-radiological.pdf

burn products and treatments for radiation injuries? In the event of a nuclear detonation, a triage scheme will be based on the likelihood that a patient will benefit from treatment. Scarce resources are best used to treat patients with low-to-moderate radiation exposure; patients with lower exposure can be released and monitored remotely or self-monitored, and patients with severe radiation exposure are best served with palliative care. By studying past radiation exposures, planners have determined that the range of radiation exposure for which patients have the best response to treatment is ~1.0–8.0 Gy.

The models can be used to assess the expected number of people who fall into various severity of injury categories (Fig. 1).[50] For example, for a detonation in New York City, damage and fallout zones can be established, and the number of patients at risk can be estimated. In the moderate damage zone, over 50% of the individuals will be prompt or expectant fatalities, with about a third of individuals being at-risk, but with the greatest chance of being successfully treated. In the light damage zone, more than 80% of individuals will be uninjured; or expected to recover with no treatment; with about 11% expected to be in the population that would benefit from treatment. The likelihood of prompt or expectant fatalities are close to zero in the wide fallout zone, but some (~7%) may be at-risk and will respond to treatment.

The modeling of radiation exposures has uncovered both opportunities and challenges. For example, planners note that sheltering in place in the fallout zone can reduce exposure to ionizing radiation and reduce the number of possible casualties, the time when it is safe to evacuate would depend on the level of radiation from the decaying radionuclide products. It is also possible to define staging areas just outside the hot zone; however, areas that are safe could still have detectable, but not dangerous, levels of radioactivity, and it might be tempting for responders to set staging zones too far away from where they would be of greatest benefit. As has been true for other disasters, access to patients, movement of responders and other critical personnel, transport of supplies, and movement of refugees from the disaster zone will be difficult due to loss of infrastructure, including roadways. All these factors, including the need for reliable methods of determining levels of radiation exposure, require careful planning and communication among partners in federal and state governments, first responders and medical communities.

[50] https://responder.llnl.gov/training.

Assessment of Radiation Exposure and Medical Preparedness for Radiological Response (J. Koerner)

Progressing from the establishment of expected injury and care scenarios, additional USG planning has gone into maximizing the ability to assess and treat injuries – radiation and otherwise. It is first important to determine the physical damage and fallout zones, to know the safe perimeters where patients can be transported for assessment and initial treatment. Patients with overt physical injuries – burns, cuts, and other trauma – can be assessed rapidly, but the determination of who will need treatment from radiation exposure among thousands or hundreds of thousands of potential patients with no outward symptoms of radiation exposure is much more challenging. Responders will likely be resource-limited (*2*), and it is critical to provide care to those who will most benefit, such as those who received 1.0–8.0 Gy of radiation without other confounding injuries.

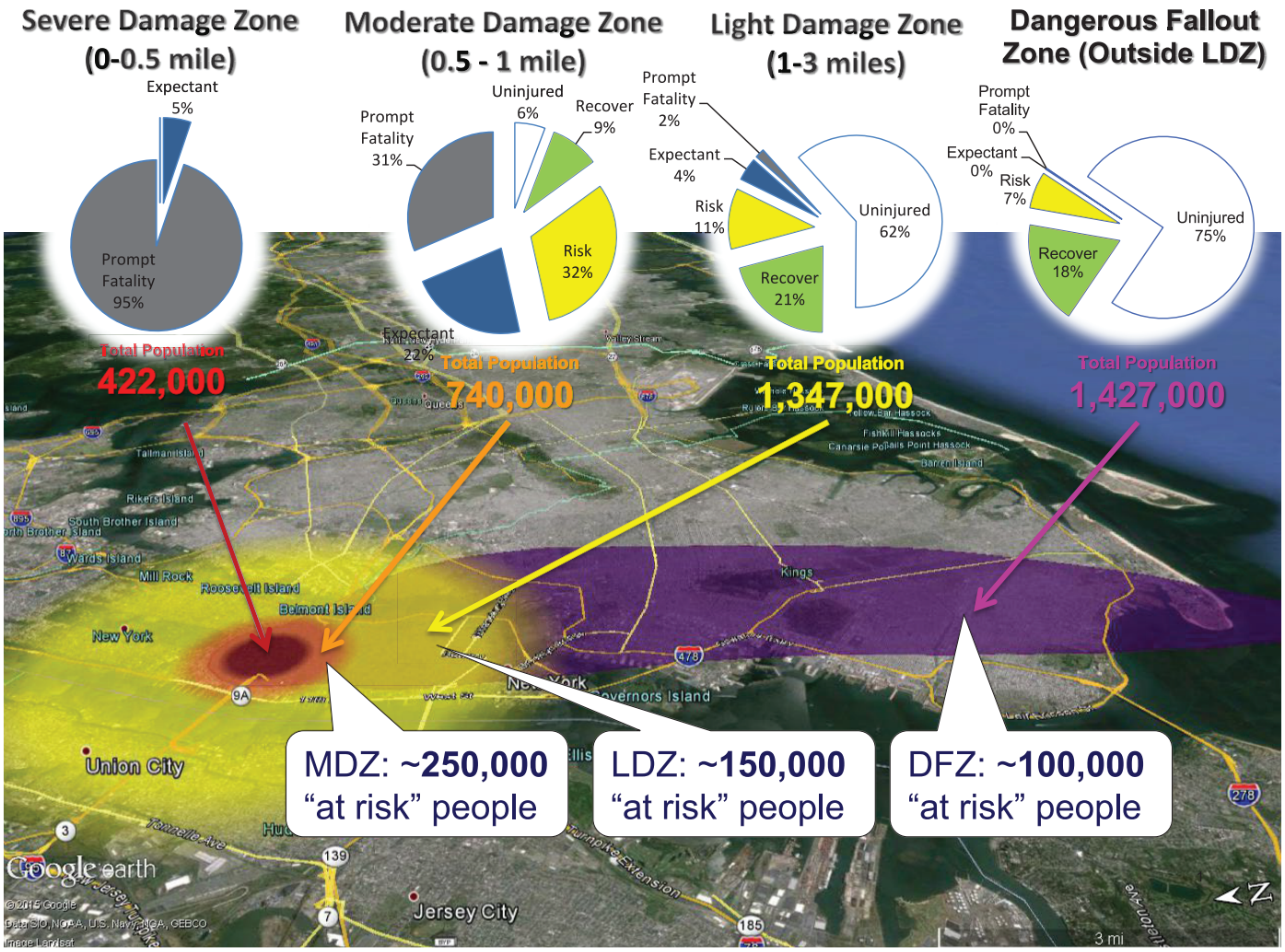

FIG. 1. Casualties in the various damage zones after a nuclear incident. The scenario used in this example is a ground-burst 10 kT bomb set off in Times Square in Manhattan, under atmospheric conditions that carried dangerous fallout southward. Figure used with permission from: Medical Needs in the Aftermath of Nuclear Terrorism (NYC Ed), Lawrence Livermore National Laboratory, LLNL-PRES-677346, 2015.

To address screening needs in the wake of a radiation public health emergency, a USG interagency working group developed the Radiation-specific TRiage, TReatment, Transport system (''RTR'') (*3*). This effort is designed to optimize resource allocation (material and personnel) to the most appropriate staging zones. Sites will be located at safe distances from the epicenter and can focus on different types of care. For example, responders at sites closer to the epicenter can focus on immediate care of blast and burn injuries, with definitive care provided in more distant facilities. Radiation injuries can be assessed farther from the epicenter and patients can then be sent to regional collection and transport sites for further care. Inherent to this planning is the need to provide continued monitoring. The early response, including assessment of injuries, will be done by local responders, since it will take time for federal officials to coordinate with local groups to evaluate needs and position assets. As part of the immediate response, personnel at health care centers that are in the region of the epicenter of an explosion, but outside of the damage zone, will be advised to shelter in place and be prepared to care for patients who need immediate care. At the first level, triage entails identifying patients who have potentially fatal injuries and directing them to treatment in regional centers. The next level of triage is to use available biodosimetry devices (*4*) to identify patients who have been exposed to radiation at the 1.5–8.3 Gy range. The goal of this level of triage is to direct scarce resources to those individuals who will benefit the most (*5*); others will be released for observation or provided palliative care, depending on the severity of exposure.

For a wider, federally driven response, local officials can access the National Disaster Medical System (NDMS), which deploys personnel and augments local responders and health care systems with Veterans Administration hospitals and hospitals within the NDMS network, including the Radiation Injury Treatment Network (RITN). As care expands from community reception centers into national networks, patient monitoring and injury assessment will take place at all levels, so that patients can be directed to

facilities capable of providing the most appropriate care. Despite these networks, an initial large surge of patients will require many more functioning care facilities. For this reason, the ASPR is setting up programs for the Regional Disaster Health Response System.[6] The goal of the system is to handle surges from any large-scale medical disaster using existing health centers working together.

Critical elements for any medical response system are ensuring communication, addressing behavioral health, and educating and training responders. Early and accurate communication among responders, health care systems and governments, as well as the public, for example, who should shelter and who should evacuate, is essential. It is also important to address behavioral health, such as patient mental trauma, and stress and concerns of care providers so they can be engaged and effective. Education and training of responders, healthcare practitioners, supply providers, and allied staff before any large-scale disaster is essential. Training should also be sustained, so that skills and standard operating procedures are current and familiar. In considering the need for continued medical monitoring and patient management, planners also anticipate large-scale hematology needs, as well as follow-up care and long-term monitoring. Any response to a nuclear disaster will require a large and coordinated effort by local responders and providers, up to regional and national receivers, to care for patients. The USG is continually working to refine and integrate systems to build the capacity for short-and long-term responses to a radiation incident, to define the goals and decisions necessary to achieve these goals, and how to assemble resources and entities that will coordinate and implement a disaster response, to save lives.

SESSION II: Animal Models for Radiation Studies

In conducting radiation exposure studies in animal models, it is important to first start with an understanding of radiation exposure and what outcomes to expect.

Animal Models for Acute Radiation Subsyndromes (K. Thrall)

It is well known that probability of survival decreases as the radiation dose increases, with higher lethal doses (5 Gy and above in humans) leading to death in hours to days or weeks, and lower lethal doses (3.5–5 Gy in humans) resulting in survival times of weeks to months. The focus of this session centered on hematopoietic (H), gastrointestinal (GI) and lung effects, and the importance of testing MCMs in animal models in accordance with the U.S. FDA ''Animal Rule'' (*6*) (21 CFR 314.610 (a) for drugs and 21 CFR 601.91(a) for biological products). The U.S. FDA is clear that the appropriateness of the selected animal model for well-controlled efficacy studies is critical, and the choice of species must be made based on the disease of interest and the drug's anticipated mechanism of action. Radiation and drug effects in the animal model should be predictive of the radiation and drugs effects in humans and should generally be demonstrated in more than one animal species. However, the U.S. FDA does not define a particular model that would be appropriate and predictive for an MCM, but instead, leaves those details for the product sponsor to propose. For any MCM that will seek approval/licensure via the Animal Rule the critical path involves carrying out of early proof-of-concept experiments through pivotal animal studies. Because it is unlikely that a drug will be approved using a single model, it is important to consult early and often with the U.S. FDA, to avoid wasting development costs and time on models that might not be acceptable to the agency.

When developing an animal model for MCM efficacy studies, it is important to acknowledge the ways that animal models may vary from anticipated, real world exposure scenarios. For example, in a nuclear incident, there will be variable absorbed doses, the radiation exposure is unlikely to be uniform, there will be a mixed population of exposed individuals, and there could be variable medical management available and in use. In contrast, studies in an animal model often utilize uniform exposure fields (e.g., bilateral, mid-line tissue dose, etc.), with health physicists and dosimetrists ensuring that the radiation exposures of different animals are as close to identical as possible. In addition, bone marrow shielding of the animal model is often included to extend survival to investigate different sub-syndromes such as GI-ARS. Efficacy is often assessed at a particular radiation exposure geometry and lethality level [e.g., the lethal dose (LD) where 50% (LD_{50}) or 70% (LD_{70}) of the animals would be expected to succumb to irradiation mortality within pre-determined time postirradiation]. Supportive care (discussed in more detail below) is generally well-defined for either small or large animal models, and in the early stages of study, research often focuses on a single sex.

Many small animal models (e.g., mouse, rat, guinea pig) are detailed in the literature, including those for total-body irradiation (TBI) H-ARS (*7*) and GI-ARS; partial-body irradiation (PBI), GI-ARS; whole-thorax-lung irradiation (WTLI) exposure for lung effects; renal and other delayed effects of acute radiation exposure (DEARE); and cutaneous radiation injury (*8, 9*). All of these models can be further influenced by factors such as age, species (e.g., mouse, rat, etc.), strain of animal, vendor, use of antibiotics in the model, means of irradiating [e.g., bone marrow shielded, or focused irradiation plus TBI (''top-off'' model) (*10*)]. Early discovery work can often be carried out in small animals, where factors such as product formulation, radiation level, timing, dosage level, frequency of drug dosing, and route of administration can be compared.

For a large animal, resources are more limited and costly, so it is important first to have worked out the parameters in small animals. As with rodent models for radiation injuries,

[6] https://www.phe.gov/Preparedness/planning/RDHRS/Pages/default.aspx.

large animal models [e.g., nonhuman primates (NHP), mini- or full-size pigs, canines, etc.] also exist for TBI H-ARS (*11*), TBI GI-ARS (*12*), PBI GI-ARS (*13-15*), WTLI for lung (*16*), TBI kidney[7] (*17*) as well as for cutaneous radiation exposure (*18, 19*). Although some aspects of radiation injury studies are easier to do in the small animal, shielding studies and provision of advanced levels of supportive care are more readily done in a larger model. For example, it may be advisable to provide higher-end support such as the administration of growth factors in an NHP to allow survival past H-ARS and monitoring of other complications like GI- or lung-driven morbidity or mortality. As for cutaneous radiation injury, porcine skin is considered to be very similar to human skin (*20*); therefore, a cutaneous radiation injury model was developed in Yorkshire swine exposed at focal areas to increasing doses of radiation. Scoring of resulting skin damage (e.g., erythema and dry or moist desquamation) was used to better understand the dose response and time course response of when the injuries occur in the model, how they present and progress, and how scoring of the injury sites can be done.[8]

Another aspect that provides confidence in the selected animal is the ability for effects in the model to be reproduced elsewhere. For example, in an inter-laboratory comparison of the radiation dose response relationship to survival in a TBI-NHP model with full supportive care, the $LD_{50/60}$ of NHPs as conducted by the University of Maryland, Baltimore was estimated to be 7.54 Gy. The $LD_{50/60}$ of the same species and strain of NHP studied at Altasciences Clinical Research was estimated to be 7.43 Gy (*21*). Even though the Altasciences study was done six years later, the same exposure and medical management protocols were used. In another model, the Göttingen minipig, BARDA also harmonized radiation exposures for ARS across multiple laboratories and was able to generate reproducible survival curves at different locations.[9] It is however, important to keep in mind the strain of animal and its characteristics; for example, the Göttingen minipig is quite sensitive to radiation effects, whereas the Sinclair strain may be less-sensitive, even though both are outbred strains (*22*).

The level of supportive care provided, especially in an NHP, can have a substantial impact on survival. For example, three radiation lethality profiles were studied in the NHP with different levels of medical management: 1. minimal supportive care (only analgesics given), yielded an $LD_{50/60}$ of 6.19 Gy; 2. standard support, with enhanced medical management (anti-emetics, anti-diarrheal drugs, antibiotics, analgesics, and nutrition but not blood transfusions) provided on days 3–30 regardless of indication led to an $LD_{50/60}$ of 7.05 Gy; and 3. full support (anti-emetics, anti-diarrheal drugs, antibiotics, analgesics, nutrition, and blood transfusions) with trigger-to-treat medical management based on individual animal symptomology generated an $LD_{50/60}$ of 7.43 Gy. From these findings, it is clear that changes in levels of support can lead to dramatic differences in postirradiation survival (*23*).

Shielding of portions of the bone marrow (e.g., 2.5–50%) can also shift lethality curves. As was seen in prior studies, 50% shielding of the bone marrow of a TBI-NHP model, provided standard support, led to an increase in the H-ARS $LD_{50/60}$ from 7.05 to 12.64 Gy. The level of shielding can also make a difference; for example, NHP hemibody with 14 Gy irradiation (standard support) yielded similar survival in a 5% bone marrow shielding at 12 Gy (full support) (*24*).

It is anticipated that no drug will be developed using a single model, and each syndrome may require a separate animal model system. However, while subsyndrome models provide valuable insight during the development process, pivotal studies may require systemic approaches that capture the biological impact of multi-organ injuries.

NHP Animal Models for Radiation Biodosimetry Advancement (L. Watthen)

The goal of BARDA is to form unique public-private partnerships with industry to develop and study vaccines, therapeutics, and diagnostics for chemical, biological, radiological or nuclear (CBRN) threats. BARDA's funding model incorporates flexible authorities, multi-year support to promote innovation, facilitate partnerships, and provide cutting edge expertise. To date, Project BioShield has supported 27 radiation products, with 14 added to the Strategic National Stockpile (SNS), and eight presented to the U.S. FDA for approval/licensure/clearance to treat ARS and other radiation injuries. In the radiation mission space, these products have included stockpiling of ThyroShield® (potassium iodide oral solution), calcium- and zinc-diethylenetriamine pentaacetic acid (DTPA), Neupogen®, Neulasta® and Leukine®.[10]

BARDA also supports a robust portfolio of funding in the area of radiation biodosimetry. Devices under development have been broadly grouped into two categories. These include point of care (POC) triage screening tests, which are simple assays to discern individuals needing medical evaluations from those who can evacuate (generally a 2 Gy threshold for treatment using a finger-stick of blood); and high throughput (HT) laboratory tests, which more accurately report absorbed radiation dose an individual received and inform further care (and could require a

[7] Brown DL, Measey T, Donini O. Radiation-induced renal changes in the Göttingen minipig. Poster presentation, 2017, 36th Annual Society of Toxicologic Pathology Symposium, Montreal, Canada.

[8] Thrall K, Manning R, Mahendra S, De Los Santos G, Fukuzaki K, Nagata R. A cross-breed comparison of cutaneous radiation injury in swine, 2015. Radiation Research Society 61st Annual Meeting, Weston, FL.

[9] https://www.medicalcountermeasures.gov/media/36856/esker_radnuc-bid-2015-508-compliant-slides-v2-508.pdf.

[10] https://www.medicalcountermeasures.gov/media/36904/01_hachett_state-of-barda-address.pdf.

venous blood draw). To effectively use available biodosimetry information to evaluate a patient, POC screening (anticipated to be ~1 million people) needs to determine if patients should return home (<2 Gy exposure suspected) or be further evaluated (>2 Gy). BARDA has been working on radiation biodosimeters since 2009, with a goal to obtain regulatory approval for a qualitative POC tests to triage individuals based on absorbed radiation. In addition, quantitative HT assays are also being developed to determine absorbed radiation exposure from 0 to 10 Gy that will aid in the management of individual with signs and symptoms of irradiation.

In an incident involving detonation of an improvised nuclear device (IND), a large number of casualties would be anticipated, which would vary based on the size of the detonation (e.g., 0.1, 1 or 10 kT).[11] As discussed above, damage zones are defined as light, moderate and severe, in circles extending from the point of ground-zero and dependent on infrastructure damage. Affected individuals could also suffer from mechanical trauma, thermal burn, radiation exposure, and/or combined injuries. The emergency response will have to take into account the ''worried well'' (concerned citizens without radiation exposure) who request medical services as well as those who have been actually exposed to significant radiation (*25*). In addition, based on the 2010 census pediatric casualties (aged 0–17 years old)[12] are predicted to make up 24% of the victims. BARDA is also working on the development of thermal burn products since combined radiation injuries would be expected to reduce survival (*26*).

There are several biodosimetry approaches at different stages of development (*27*), however, there are currently two primary methods available to inform treatment of suspected radiation victims. These are the dicentric chromosome assay (DCA), and lymphocyte depletion kinetics (*28*). The DCA is an important tool but it has some drawbacks that make its use challenging during a mass casualty radiation emergency (*29*). For example, the assay has large inter- and intra-assay variation, is only feasible up to 4–5 Gy (not consistent at higher doses), requires 72 to 96 h for cellular incubation (difficult to tie results back to the patient), necessitates slide preparation, and reading of test results is currently not routine in any U.S. laboratory (few labs with the capability exist, with limited sample ability).

As with the DCA, reliance on lymphocyte depletion kinetics to accurately estimate radiation dose received can be problematic since it would depend on pre-exposure counts which can vary by person from $1.0–3.0 \times 10^9$/L (highly variable). In addition, for greatest precision, the test requires a minimum of two, or preferably, three lymphocyte counts (at least 6 h apart) over a few days, and an accurate assessment is not possible when the lymphocyte count falls below1×10^{-6}/L (*30*). It is estimated that 4 Gy and higher exposed casualties will drop below this lymphocyte count level in 3–7 days. Relying solely on postirradiation symptoms may be problematic as well since early symptoms such as vomiting, and diarrhea will not be developed by all exposed to radiation and some unexposed may develop them due to other factors. Although the geographical location at the time of the blast can help to estimate absorbed dose, differences in shielding can result in major dose variation where a person can be four feet from another person and receive a much different dose.

The ideal biodosimetry target product profile (TPP) differs for POC and HT screening assays. The POC device is designed to be a sorting tool intended for austere settings (tents, shelters), with accuracy over 7 days. For this device, no training should be needed, and a finger-stick blood drop is preferred. For the HT devices, accuracy of ~0.5 Gy is desirable, but this is a high bar. The assays must be accurate over a large range of exposure doses and should be able to be run in an existing medical laboratory network. BARDA anticipates needing to screen 400,000 individuals within 7 days with HT devices.

For regulatory strategies to move these approaches forward, it is more difficult for devices since there is no U.S. FDA Animal Rule on which to rely. BARDA has assumed that several models will be instrumental in getting device clearance from the U.S. FDA. These have included: 1. an NHP model exposed to a single radiation dose *in vivo*, 2. an NHP model exposed to fractionated irradiation (to bridge to humans) and, 3. patients receiving fractionated irradiation prior to stem cell transplant. Although the use of clinical human samples is not ideal because fractionation could produce different damage, it is critical to show that NHP and human fractionated exposures are similar enough to believe the tests are valid. In addition, confounders such as prior chemotherapy or other treatments could impact the results. Historically, funded models have attempted to demonstrate similarity of gene, protein, or cytological responses to single and fractionated dose irradiation across species (*31–33*). Some of this work has resulted in pre-Emergency Use Authorization (EUA) from the U.S. FDA. BARDA together with industry partners, continues to pursue the first biodosimetry *in vitro* diagnostics approval.

Once developmental work is completed, a biodosimetry pivotal testing process involves intense pre-validation of an assay, using samples from normal humans of all ages with percent ethnicities representative of the U.S. population. These affected populations could also include individuals with potentially confounding conditions such as being immuno-compromised, or pregnant, with trauma, burn, or diseases like diabetes, rheumatoid arthritis, sepsis, etc. Genes have been chosen to attempt to rule these disease-specific or health-specific genes out. To determine the

[11] NSC, 2010, Planning guidance for response to a nuclear detonation, available at http://www.remm.nlm.gov/PlanningGuidanceNuclearDetonation.pdf.

[12] https://www.census.gov/prod/cen2010/briefs/c2010br-01.pdf.

effects of radiation and MCM administration on genes, proteins, or cytology, samples have been collected from pre-transplantation patients receiving fractionated irradiation, NHPs receiving TBI either in single or fractionated doses, and both humans and NHPs after G-CSF or Leukine administration. In addition, a host of common substances can be spiked into human blood and tested for potential assay interference [e.g., bilirubin, human serum albumin, human immunoglobulin (IgG), L-ascorbic acid, hemoglobin, acetylcysteine, captopril disulfide, and others depending on the assay chemistry].

Among the many specific regulatory challenges is the need to demonstrate biodosimetry test accuracy (goal of ± 0.5 Gy is probably not achievable), while also achieving sufficiently low false positive (FPR) and false negative (FNR) rates on qualitative biodosimetry tests. There are also issues with comparability of human to NHP data, to achieve a high level of similarity between the two species. There is no ethical way to conduct a clinical trial to obtain human samples for test validation, and there are issues with available clinical patients, because humans with leukemia and the previous chemotherapy are a difficult comparator group (even though there are specific inclusion and exclusion criteria in the protocols). Most other cancer patients are dosed with small irradiation fields, which is not similar to a nuclear detonation scenario. Although TBI fractionated irradiation data is quite similar between species, peak responses in the species may differ in timing and fold-change, which must be considered.

Fully understanding the clinical utility of a biodosimetry test to manage individual patients is distinctly different than managing an estimated 400,000 (for HT) up to 1,000,000 (for POC) people. Having a triage tool to separate concerned citizens from individuals with medically significant doses is important to move the injured into the medical system, and having a laboratory test to report an approximate absorbed dose will facilitate differentiation of potentially confusing symptomology for physicians. Patient reports need to have sufficient information for the medical staff to understand the biodosimetry test result, which can follow the patient to all the medical centers that they will encounter in their quest for treatment.

Appropriately modeling the nuclear incident (e.g., dose rate, gamma/neutron ratio, partial/whole body irradiation) can only be achieved with appropriate instrumentation. For example, it is not possible to model the dose rate of prompt radiation delivered in less than a minute of detonation, because many modern instruments (e.g., X-ray irradiators) are designed to ensure a low-dose rate and spare normal tissue. At most, approximately a threefold change in a typical dose rate can be achieved experimentally for administration to large animals. In addition, some situations like a gamma/neutron mix that is anticipated after detonation of an IND are difficult to model since very few research sites can deliver that kind of radiation especially to large animals. Furthermore, yields of INDs employing older designs are skewed to include gamma whereas newer bombs may have a greater neutron component, and the actual device mix of gamma and neutron can be highly variable. Clearly, endless experiment variations would be needed to truly understand the exact outcomes of a particular scenario and that is not feasible, so we must use our best approximation. Given the different locations where a detonation could occur and the density of buildings in that area, this planning can also be very difficult (*2*).

Qualitative POC biodosimetry devices with BARDA support include a protein expression immunoassay that is a dual, lateral-flow technology with a reader and cell extractor. The device requires only of a finger-stick of blood, with a throughput estimated to be $\sim$24 samples per hour. These instruments can be pre-positioned close to light and moderate damage zones, with a positive or negative readout from a test strip. For HT devices, there are currently three developers, and among the approaches being supported are two gene expression assays (with only two overlapping genes for the two signatures) and a micronuclei/binucleated (sophisticated imaging) approach. Through contractual arrangements, the awardees are working with BARDA and the U.S. FDA to determine an appropriate validation data package. All four approaches have moved into Project BioShield funding,[13] and have started a formal validation process, which includes product validation and clinical testing, filing of a pre-EUA data package (one completed already), and obtaining U.S. FDA clearance. These activities are necessary to be able to fill the initial test stockpile requirement and maintain SNS readiness (now directed by HHS, ASPR).[14]

In conclusion, to enhance radiation preparedness and save lives, BARDA funding is advancing HT and POC biodosimetry tests by overcoming regulatory challenges to attain pre-EUA status so that tests could be used immediately in case of an incident. Furthermore, BARDA plans seek clearance for at least one test in each category and develop test implementation strategies with state and local stakeholders. The agency will continue working with the SNS group to be able to make the devices available in the right place at the right time. Looking ahead, more research is still needed to better understand and model biodosimetry markers for PBI and combined injuries. Most importantly, device readouts need to be linked to radiation exposure endpoints known to physicians [e.g., Medical TREatment ProtocOLs for Radiation Accident Victims (METREPOL)] in order to provide proper triage and treatment for patients exposed in small and medium size radiation accidents (*34*).

[13] https://medicalcountermeasures.gov/BARDA/Documents/BID2018_Presentations/Wathen_BID18_CBRN_DX.pdf.

[14] June 6, 2018, Hearing on Pandemic and All Hazards Preparedness Act, House Energy and Commerce Committee, Health Subcommittee.

TABLE 3
Poster and Oral Presentation at the Policy and Pathway to FDA Approval Workshop

Name	Title	Affiliation
Model Development		
Jackson, Isabel	A New Zealand white rabbit model of acute radiation sickness after total-body irradiation	University of Maryland
Jackson, Isabel	Hematological effects of non-homogenous ionizing radiation exposure in a non-human primate model	University of Maryland
Fish, Brian	WAG/RijCmcr rat models for injuries to multiple organs by single high dose ionizing radiation: similarities to non-human primates (NHP)	Medical College of Wisconsin
Kumar, Vidya	Development of partial-body irradiation model using small animal radiation research platform	Armed Forces Radiobiology Research Institute
Kenchegowda, Doreswamy	Development of a minipig model of cutaneous radiation injury	Armed Forces Radiobiology Research Institute
Garty, Guy	Irradiation systems modeling IND exposure scenarios	Columbia University
Medical Countermeasure Research		
Ghosh, Sanchita	A robust mouse model of hematopoietic acute radiation syndrome for countermeasure screening	Armed Forces Radiobiology Research Institute
Perez-Horta, Zulmarie	NIH/NIAID Radiation and Nuclear Countermeasures Program (RNCP)	NIAID/RNCP
Kaytor, Michael	Development of BIO 300 as a Medical Countermeasure for H-ARS and DEARE-lung	Humanetics Corporation
Norris, Andrew	Drug formulations development in the countermeasures space	BCN Biosciences
Lehtimaki, Mari	Nicotine as potential treatment to rescue vaccine immunity after irradiation	FDA
Geng, Jian-Guo	Radiation countermeasure by R-spondin 1, Slit2 and fibroblast growth factor 4	University of Michigan
Day, Regina	Senescence in response to thoracic irradiation in mice	Uniformed Services University of the Health Sciences
Biomarker Assays and Biodosimetry Devices		
Sigal, George	Human stem cell transplant patients as a radiation model for evaluating biodosimetry tests	Meso Scale Diagnostics, LLC.
Phillips, Gary	Bridging the gaps: Using an NHP model to predict single dose radiation absorption in humans	Duke Cancer Institute
Aryankalayil, Moly	Non-Coding RNAs as biomarkers for radiation biodosimetry: From mouse to monkey	National Cancer Institute
Menon, Naresh	Pre-clinical and clinical models for biodosimeter development	ChromoLogic LLC
Vicente, Elisabeth	Species-specific recombinant antibody development for the evaluation of radiation exposure and treatment	University of Maryland
Wright, Sammoya	Creating a mobile application for radiation exposed patients in a mass casualty scenario	Charles Herbert Flowers High School Science and Technology Program
Sproull, Mary	Assessment of a panel of radiation responsive proteins across multiple murine strains to total body radiation exposure	National Cancer Institute

SESSION III: Oral Presentations and Poster Session

The session allowed researchers to present their projects, taking into consideration the policies and regulations that drive the drug development process. For this purpose, investigators focused on how NIH policies are reflected in their research, ways to fulfill requirements of the animal rule for licensure of MCMs, guidelines for approval of biodosimetry approaches, self-identification of technology readiness levels (TRLs), and future drug development plans. This forum guided the conversation towards identifying the components needed for the critical path to licensure (Table 3). All speakers were tasked with identifying key categories of the workshop and the current accomplishments:

- NIH policy [reproducibility, robustness, biological variables and authentication of key resources (biological and/or chemical)]
- Animal models for different radiation syndromes [hematopoietic, gastrointestinal, lung, kidney, cutaneous, vascular]
- Animal models in radiation biodosimetry that bridge the gap to human data
- Technology readiness level of drugs/devices in the MCM or biodosimetry field
- Development plan for MCM following Animal rule approval considerations
- Development plan for biodosimetry devices following FDA guidance

After the poster session, brief oral presentations were presented from select abstracts, highlighting current animal models, products, and devices in the various stages of development (summarized in Supplementary Materials; https://doi.org/10.1667/RADE-21-00198.1.S1).

SESSION IV: NIH Policies and FDA regulatory Guidance

NIH Policy to Enhance Reproducibility through Rigor and Transparency (P. Valdez)

Advancing products through licensure and commercialization requires an understanding of the regulations governing drug development. The goal of the regulations (and their governing statutes) is to ensure the end-user receives the safest and most effective products currently available for the specified indication. For a drug, it means that it will reproducibly address a pathology as a therapeutic or prophylactic medication; for a device, it will reproducibly function as intended, be it an instrument of life support, a diagnostic kit, or a tool for conducting the practice of medicine. Above all, it must be safe. The potential for adverse events (i.e., ''side-effects'' or failure modes) is to be understood, and if possible, controlled. Collectively this is the concept of ''quality,'' and should be incorporated into every facet of drug and device development, from research through clinical trials and post-market surveillance.

In 2005, John Ioannidis presented an alarming report describing a decline in the overall quality of published scientific research, questioning the veracity and reproducibility of research findings (*35*). Eleven years later, Baker published survey results which indicated that 90% of researchers polled agreed that there exists a reproducibility crisis, with more than half calling it significant (*36*). When asked about reproducing another scientist's experiments, 70% answered that they were unable to do so. Among the top factors cited was ''low statistical power or poor analysis.'' This observation agrees with Ioannidis, who found that ''Research findings from underpowered, early-phase clinical trials would be true about one in four times, or even less frequently if bias is present.'' Numerous other reports and commentaries have provided concurrence (*37–41*).

A workshop convened by the National institute of Neurological Disorders and Stroke (*42*) performed a gap analysis on preclinical studies to ascertain causes of deficient reporting and to propose solutions. Workshop stakeholders determined that in many cases, sample size estimates, blinding, randomization, sex, and transgene copy numbers were not being reported. Further, the workshop raised ''the concern that the reviewers of these studies could not adequately identify potential limitations in the experimental design and/or data analysis, limiting the benefit of the findings.'' A key result of the workshop was the recommendation of reporting standards that ultimately led to the drafting of an NIH policy for rigor and transparency. The burgeoning initiative was not lost on publishers of major journals, who began implementing changes to review practices, including verification of experimental design and more thorough review of statistical methods (*43*). The focus of the policy is to promote increased rigor and transparency as easy-to-measure short-term goals, and thereby improve reproducibility over the long term. The principles to guide policy development:

- Clarify NIH's long-standing expectations regarding rigor and transparency in grant applications
- Raise awareness and begin culture shifts in the scientific community
- Improve the way applicants describe their work to provide sufficient information for reviewers
- Ensure that NIH is investing in the best science and minimizing unnecessary burden

Implementation was announced in 2015[15,16] to begin enforcement with grants submitted in January 2016, with further clarifications implemented January 2019.[17,18] The NIH policy acknowledges that all research builds upon prior studies. Thus, applicants should critically assess strengths and weaknesses of the prior investigations that serve as key support to the proposed project and describe how the proposed research will address these weaknesses. Specific considerations include review of blinding strategies, repetition, adequacy of positive and negative controls, appropriate statistics, relevant biological variables, and authentication of key resources.

Applicants should describe the overall strategy, methodology, and analyses to be used to accomplish the specific aims of the project. Specifically, the experimental design and methods proposed should describe how they are designed to obtain robust and unbiased results. Similarly, reviewers are to assess whether the experimental design is well-reasoned and appropriate to accomplish the specific aims of the project. Furthermore, investigators must present sufficient strategies to ensure a robust and unbiased approach. Potential problems, alternative strategies and benchmarks for success should be included. Risks should be identified, assessed and addressed with thoughtful management and mitigation plans.

Biological variables such as sex, age, weight, and underlying health considerations are often critical factors affecting health or disease. In 1993, the NIH Revitalization Act (Public Law 103-43)[19] was passed, making the inclusion of women in clinical trials a requirement by law. However, analogous efforts in pre-clinical work have not been adopted, resulting in inadequate inclusion of both sexes, creating an absence of data to assess sex differences and contributing to the rise of irreproducibility (*44*). In accordance with the new policy, investigators need to describe how sex is factored into experimental design and must provide a strong justification to limit a study to one

[15] https://grants.nih.gov/grants/guide/notice-files/not-od-15-103.html.

[16] https://grants.nih.gov/grants/guide/notice-files/not-od-16-011.html.

[17] https://grants.nih.gov/grants/guide/notice-files/NOT-OD-18-228.html.

[18] https://grants.nih.gov/grants/guide/notice-files/NOT-OD-18-229.html.

[19] https://www.congress.gov/bill/103rd-congress/senate-bill/1.

sex. Similarly, reviewers are looking for how other biological variables are being addressed in the experimental design.

Finally, investigators should provide a plan to authenticate and insure the identity and validity of key biological and/or chemical resources. Key means integral to the research and have qualities or qualifications that could influence the research data. Examples include cell lines, specialty chemicals, antibodies, and other biologics. Standard laboratory reagents such as buffers, chemicals, and common biologicals (e.g., albumin) are not expected to vary and need not be considered ''key.'' Note that hundreds of cell lines have been reported to have been misidentified (*45*). In addition, cultures can become contaminated with viruses, mycoplasma, or other agents that can alter their behavior, or they can experience phenotypic changes over time resulting from mutations, chromosomal duplications and/or rearrangements, and epigenetic factors (*45–47*). Managing key resources is tantamount to improving rigor and transparency.

Investigators are responsible for rigor and authenticity; NIH has resources available for investigators. The NIH Office of Extramural Research provides the Rigor and Reproducibility[20] policy on its website, as well as descriptions of the application guidelines. Additionally, training modules are provided on the National Institute for General Medical Sciences website.[21]

Radiation Biodosimetry Development and Validation Challenges: Regulatory Perspective (F. Reyes-Turcu)

As described in session I, a radiation mass casualty event, such as a 10 kT nuclear detonation, can impact more than 1,000,000 people that need to be evaluated for radiation exposure and/or contamination[22] (*48, 49*). Given the potentially large numbers of people to be processed, and the time-sensitive nature of the therapeutic window for MCMs, radiation dose assessment will require a multi-phased, multi-parametric approach.

Radiation biodosimetry devices are a subset of *in vitro* diagnostics (IVDs) that can be used to estimate the absorbed radiation dose received by individuals (*50–52*). POC devices to screen all victims will need to have low false negative results to ensure that all who were exposed to dangerous radiation levels are properly triaged. HT dosimeters will screen those in the treatment centers to further refine exposure sorting. These devices can be designed using various technologies, such as multiplexed immunoassays, or molecular and cytogenetic-based approaches. Assays will also be needed for clinical management and patient follow-up; low false positive rates are important here to avoid further treatment of patients who might no longer need it. Quantitative outputs need to be accurate and qualitative around clinical decision points. Patients will have a critical need for the right treatment, therefore erroneous results should be minimized.

This list of desirable specifications creates unique device development challenges. Intended use locations can vary from temporary triage sites with relatively untrained users to major medical centers. The intended use population is potentially broad, the response to radiation injury in a diverse population is complex and many human factors such as demographics, health impact, and biomarkers are not well understood.

These development challenges also come with regulatory challenges, such as determining the path to market and identifying pivotal validation studies that need to be conducted. Fortunately, guidance is available from the FDA to help address these needs (*53*).[23] The regulations for medical devices are provided in 21 CFR, Parts 800-1050. In addition, developers should refer to general medical requirements found in Parts 1–99 of 21 CFR. The Agency's current thinking on applying the regulations is made available via Guidance Documents;[24] of interest are the Radiation Biodosimetry Guidance (UCM427866) and the Pre-submission Guidance (UCM311176). Using the Guidances and Regulations the product Sponsor can develop a proposed path to market; together with information regarding the device, the Sponsor can request a meeting with FDA to discuss their plans and obtain advice from the agency. The Agency will wish to review the device description and intended use as well as plans for analytical and clinical validation testing, and depending on the stage of development, any validation results the Sponsor already has. Note, that pivotal validation studies should be conducted using the final test configuration. With the information presented, the Agency will help to classify the device based on risk and the extent of regulatory controls required. In general, the regulatory controls will depend on product area requirements, instrument controls to foster predictably safe and effective medical devices, and risk which will indicate the appropriate level of regulatory oversight and help guide the Sponsor's regulatory strategy. Device classification may be generalized (Table 4), but sponsors are reminded that classification is complex, and it is advised that sponsors thoroughly review the Guidance and regulations and discuss their strategies with the Agency.

The next question to resolve is whether the device has a well-defined, safe, and effective ''predicate'' (a previous version that has been cleared for marketing); the sponsor must demonstrate substantial equivalence, that is, the new device is at least as safe and effective as the predicate.

[20] https://grants.nih.gov/policy/reproducibility/index.htm.

[21] https://www.nigms.nih.gov/training/pages/clearinghouse-for-training-modules-to-enhance-data-reproducibility.aspx

[22] https://www.phe.gov/Preparedness/planning/playbooks/stateandlocal/nuclear/Pages/background.aspx.

[23] https://www.fda.gov/emergency-preparedness-and-response/counterterrorism-and-emerging-threats/medical-countermeasures-initiative-mcmi.

[24] www.fda.gov/Regulatory information/Guidances.

TABLE 4
Medical Device Classification

Class	Risk	Controls	Submission
I	Lowest	General[1]	Exempt* 510(k)
II	Moderate	General and special (if available)	Exempt 510(k)*
III	Highest	General and PMA	PMA

* More common submission requirement of this class.
[1] General controls include labeling, reporting, Establishment Registration, Quality System, etc.
[2] Special controls include design characteristics/specifications, testing, special labeling, etc.

Otherwise, the sponsor must fully demonstrate the safety and effectiveness of the device through a premarket approval application (PMA). If the device has no existing classification regulation, that is, no predicate, the Sponsor may proceed through the de novo classification pathway. Introduced into law through the FDA Modernization Act (1997),[25] de novo created new classification regulations and provided a marketing process for novel devices. Typically, device technology without a viable predicate, are defaulted to class III; de novo classification provides a mechanism for classifying a device into either class I or II, when appropriate and the risks can appropriately be mitigated with either general controls (GCs) or GCs and special control (SCs). The majority of de novos which are authorized are designated as Class II; however, some de novos may be denied because the risks cannot be appropriately mitigated via GCs and SCs and therefore will require PMA as Class III devices.[26]

Once the regulatory pathway has been defined and sufficient valid scientific evidence has been developed, the Sponsor prepares their premarket submission. Each type has particular processes, applicable regulations and guidance, review times, and evidence burden.

- Investigations
  - ''significant risk'' studies require an Investigational Device Exemption (IDE)
  - ''non-significant risk'' studies and those exempt from 21 CFR 812 only require IRB approval
- Premarket Approval (PMA)
- Premarket Notification
  - 510(k) clearance – requires substantial equivalence between new device and predicate in regard to intended use, device features, and performance testing
  - de novo authorization – creates potential alternative to PMA depending on risk-benefit profile
- Humanitarian device exemption (HDE) – a marketing application for a Humanitarian Use Device (a device intended to treat or diagnose disease or condition that manifests in not more than 8,000 individuals)
- Emergency Use Authorization - Some devices, including biodosimetry devices, may qualify for an Emergency Use Authorization (EUA), permitting use of an unapproved product during a declared emergency (life-threatening or serious condition) where no alternative is available, and there is insufficient time to obtain FDA clearance, approval or licensing under the FD&C Act (*22*). Requests for EUA are submitted to the FDA Office of the Commissioner.

Regulatory submissions to obtain clearance, authorization, or approval for a device or IVD should include descriptions of the device (platform, components, software, limitations of the technology), intended use/indication [including the analyte, specimen type, population (e.g., pediatric)], setting of use (e.g., field triage, professional use, output, and the appropriate timeframes for testing), performance (specimen handling, pre-analytical, analytical, and clinical), instrumentation and software validation,[27] and labeling. For a PMA, the submission should also describe the manufacturing, design controls, and quality system requirements (21 CFR 820). A radiation biodosimetry device may also include explicit warnings and disclaimers such as limitations and need for radiation dispersal monitoring.

Validation, the process of demonstrating that the device or IVD will work as intended, carries some unique challenges during development of radiation biodosimetry devices. Appropriate samples are often difficult to obtain and may necessitate alternatives, such as samples from cancer patients undergoing radiation therapy, use of contrived specimens such as spiked samples, *ex vivo* irradiated samples, or animal-derived samples. Animal models need to be carefully chosen and may be used when the analyte is not stable in archived or contrived specimens, adequate specimens are not available from specimen banks, or a prospective study is either unethical or unable to generate an adequate sample set. Sponsors are encouraged to review the Animal Study Considerations in the FDA Guidance for Radiation Biodosimetry Medical Countermeasure Devices (*53*). The Guidance discusses considerations for defining the model, animal care and use, and confounding factors (such as housing conditions, diet, environment and husbandry). The guidance also discusses important aspects of demonstrating accurate bridging between human data and the animal model (including device output and error, normal ranges, kinetics) and providing a rationale for equivalent doses across species. If bridging is successful then animal studies may address device performance at conditions that cannot be addressed

[25] https://www.fda.gov/regulatory-information/food-and-drug-administration-modernization-act-fdama-1997/fda-backgrounder-fdama.
[26] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/de-novo-classification-process-evaluation-automatic-class-iii-designation.
[27] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/guidance-content-premarket-submissions-software-contained-medical-devices.

in human clinical studies such as high single doses, effects at varying dose rates, and potential confounding factors.

Finally, the Sponsor should prepare comprehensive analytical validation studies to show that their radiation biodosimeter provides reliable and accurate measurements of the intended type of clinical specimens with various sources of variability (*35, 53*). Analytical validation covers accuracy, precision, sensitivity, specificity, linearity, stability, if multiple specimen types are to be used, matrix equivalency. Clinical validation should also be considered. Normal samples can be used to inform backgrounds and evaluate confounding conditions. Prospective studies such as with TBI patients, or retrospective studies on stored samples may be used to validate outputs; however, both have limitations.

For a successful Radiation Biodosimetry Device development project, the FDA recommends early and frequent interaction, careful consideration of the path to market, consideration of appropriate mitigations (e.g., special controls) for de novo requests, and consideration of a pre-EUA submission. A pre-EUA submission opens dialog between FDA and the Sponsor, in a non-emergency setting, for additional discussions regarding the design and implementation of adequately controlled clinical trials that could be conducted during the emergency response. It also facilitates more complete EUA requests and agency review. EUAs and pre-EUA activities are further discussed in FDA's guidance ''Emergency Use Authorization of Medical Products and Related Authorities.[28]

Development of Therapeutics for Radiological and Nuclear Emergencies (L. Marzella)

MCM development for use in radiological and nuclear emergencies is a collaborative effort across the USG (including FDA, NIAID, BARDA, the Centers for Diseases Control and Prevention (CDC), and the DoD as well as many non-governmental stakeholders, with the objective of anticipating threats and developing the capacity to respond.[29] The roles of the FDA are to accelerate the development and review of diagnostic and therapeutic products, identify and address scientific and regulatory gaps (e.g., development of animal models and manufacturing issues), and above all, to ensure the safety of end-users of an MCM. In collaboration with federal partners, FDA works to strengthen communication, promote innovation, identify unmet medical needs and scientific gaps, and share national preparedness objectives and concept of operations. With industry partners, FDA reviews product development plans, anticipates difficult design and evidentiary issues, and plans evidence-based development.

The U.S. FDA is responsible for the review and approval, licensure, marketing authorization, or clearance of MCMs and devices throughout the product lifecycle. This includes monitoring MCMs for adverse events through programs such as MedWatch[30] and the Vaccine Adverse Event Reporting System (VAERS),[31] applying legal mechanisms to prepare for and facilitate emergency use, as well as for consumer protection against fraudulent claims and misbranded or adulterated products. The oversight of most drug products for radiation MCMs is managed by the Division of Imaging and Radiation Medicine (DIRM, formerly the Division of Medical Imaging Products), within the CDER. DIRM provides guidance and regulatory oversight for MCM to treat ARS sub-syndromes (e.g., bone marrow/hematological, and gastrointestinal), cutaneous radiation injuries, and delayed effects of acute radiation exposure (e.g., lung, kidney, tumorigenesis).

Traditional regulatory pathways begin with an Investigational New Drug Application (IND) and proceed through:

- New Drug Application (NDA) 505(b)(1): stand-alone application for new drugs and efficacy supplements
- NDA 505(b)(2): application that relies in part on others' data or other information
- ANDA 505(j): abbreviated application for duplicate (generic) drugs
- 351(a) of FD&C Act: Biologic License Application (BLA)
- 351(k) of FD&C Act: biosimilar or bio-exchangeable biologic products

In addition, drug developers may apply for fast-track, priority review, or breakthrough therapy programs that considerably reduce the review time for approval or licensure. Orphan product designations and grant programs are available for indications that affect less than 200,000 patients per year in the United States. Specific priority review vouchers for material threat MCMs[32] were established through the 21st Century Cures Act as an incentive for the development of MCMs. Developers of MCMs are eligible to apply for the material threat priority review voucher, which can be applied toward the development (through NDA or BLA) of other new drugs. An EUA can also be used for unapproved products or indications for use in public health emergencies in absence of adequate approved and available alternatives.

For the development of most MCMs to treat exposure to radiation, developers must rely on the U.S. FDA Animal Rule (6). The Animal Rule applies when human efficacy

[28] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/emergency-use-authorization-medical-products-and-related-authorities.

[29] https://www.fda.gov/EmergencyPreparedness/Counterterrorism/MedicalCountermeasures/default.htm.

[30] https://www.fda.gov/safety/medwatch-fda-safety-information-and-adverse-event-reporting-program.

[31] https://www.fda.gov/vaccines-blood-biologics/vaccine-adverse-events/vaers-overview.

[32] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/material-threat-medical-countermeasure-priority-review-vouchers-draft-guidance-industry.

trials are unethical or unfeasible. Important considerations when conducting animal efficacy studies include:

- Selecting animal models able to demonstrate a response to the MCM that will be predictive for humans, as well as allowing the extrapolation of pharmacokinetic (PK) and pharmacodynamic (PD) data from animals to humans to determine dosing for humans.
- Conduct of adequate and well-controlled studies in accordance with the animal welfare act, and Public Health Service policies on humane care and use of laboratory animals.
- Natural course of condition is well characterized.
- Major elements of supportive care that mimic clinical management are included.
- Adequate veterinary care is provided.

Development plans for animal efficacy studies should describe randomized studies with personnel blinded to treatment assignments. They should include detailed supportive care protocols and a complete statistical analysis plan. Development plans under the Animal Rule should carefully consider the potential for PK and PD differences between species and their potential impact on determination of the human dose. Determination of dosing and administration should consider the dosage form and route of administration, understanding that the proper dosage form for one model might not be appropriate for another. In general, at least two models are needed, with a fully effective MCM dose being established in each, and adequate bridging between the animal and proposed human doses. It may also be more appropriate to rely on PD parameters than PK for establishing that bridge. The context of use will also inform the development strategy, as pre-exposure radioprotectors, post-exposure mitigators, and decorporation agents may all have different routes of administration as well as PK/PD parameters.

Finally, but most importantly, as with all drug development, preclinical (non-clinical) safety and toxicology studies will need to be addressed in animal models. If the drug in question is being repurposed (i.e., an approved/licensed product being developed for a new MCM indication), an extensive safety profile in humans will likely already be available through clinical experience and post-marketing studies. If not available, a traditional IND will be required to conduct studies in healthy volunteers, with appropriate age, sex and race considerations.

SESSION V: Government Support for the Advancement of MCMs and Biodosimetry Technologies

The NIAID Medical Countermeasure Research and Development Program (D. Cassatt)

The mission of the NIAID/RNCP program is to support early to mid-stage research to develop radiation/nuclear MCMs and biodosimetry devices (*54*). The NIAID/RNCP uses interagency agreements (IAA), R01s and cooperative agreements, U01s, and U19s like the Centers for Medical Countermeasure Against Radiation Consortium (CMCRC) to fund early research and development projects. From 2005 through 2020, the CMCRC has published more than 1,400 publications, produced more than 50 patents, and awarded over 200 pilot projects to explore new ideas in radiation research. In addition, the CMCRC has provided a foundation for the characterization of rodent and other larger models to test MCMs for acute and delayed radiation effects.

Advanced product development at NIAID/RNCP is supported by several mechanisms, including a Product Development Support (PDS) contract, Small Business Innovation Research (SBIR) grants, product-focused Broad Agency Agreement (BAA) contracts, and the Armed Forces Radiobiology Research Institute (AFRRI) Interagency Agreement (IAA). While all these mechanisms are designed to fund advanced development of a lead candidate, the PDS and AFRRI are particularly designed to test efficacy of MCMs using well-characterized animal models. The PDS was awarded to the University of Maryland from 2005–2015, with awards to SRI International from 2015 to present. During this time, rodent and NHP models of H-and GI-ARS have been developed (*12, 23, 55*). In addition, animal models for DEARE continue to be developed for GI and lung injury (*56–59*). Rat and canine models have also been established to test radionuclide decorporation agents (*60–63*). Under the PDS, one oral decorporation IND was obtained, three MCMs were manufactured/formulated, and three MCMs – Neupogen and Neulasta (2015) and Nplate (2021), were approved by the FDA for H-ARS. The PDS contract has also been used to spearhead efforts to help advance biodosimetry devices by providing valuable NHP samples to developers for proof of principle analysis (*64*).

As highlighted above, regardless of the funding mechanism or stage of product development, the four pillars of the Animal Rule – mechanism, pivotal studies, primary endpoint and selection of human dose – must be addressed (*6*). The NIAID/RNCP company engagement pathway begins with an introductory teleconference followed by a Radiation and Nuclear Group – Advanced Product Development (RNG-APD) meeting that allows for a more comprehensive consideration of the potential MCM. The RNG-APD is an interagency meeting [NIH, BARDA, DoD, CDC, ASPR, FDA, The National Aeronautics and Space Administration (NASA), AFRRI and SRI] designed to obtain product development feedback at an early stage. During this set of meetings, guidance and the best drug development pathway is established.

Regulatory Affairs and the Role of DAIT ORA in Advancing MCM and Biodosimetry Products (P. Price)

Establishing a regulatory pathway necessitates at least a basic understanding of regulatory compliance. In the U.S., the primary regulatory agency is the FDA whose mission is

the protection of public health and ensuring the safety, efficacy and security of drugs, biologics, and medical devices. In the U.S., Congress writes the laws which are incorporated into the U.S. Code. To accomplish its mission, FDA interprets the law into regulations which are published in the Code of Federal Regulations and enforced as law. To assist sponsors and developers, the FDA drafts guidance to represent the Agency's best current thinking on a topic area. While these are not enforced as law, if the guidances are followed, the sponsor should remain in compliance with the regulations.

A few of the most relevant laws and regulations were discussed, including Public Health Service Act (42 USC 262-263),[33] Federal Food, Drug and Cosmetic Act (21 USC 301-392),[34] FDA Modernization Act (for medical devices like biodosimeters),[35] FDA Administration Amendments Act (pediatric use),[36] and FDA Safety and Innovation Act (generic and biosimilars),[37] and the Code of Federal Regulations (CFR). The objective being to provide a legal background for developing regulatory approval pathways. Regulatory approval means all approvals from the FDA or other U.S. regulatory authority necessary for the commercial manufacture, marketing and sale of a product in the United States in accordance with applicable law. The types of approvals (e.g., approvals, licensures, authorizations, registrations, and clearances) for drugs and biologics were presented previously by Drs. Reyes-Turcu and Marzella. The role of DAIT ORA is to work with the awardees of DAIT NIAID grants/cooperative agreements and contracts, including those awarded through the RNCP, to navigate the regulatory process.

For drug compliance, the first step is an IND application. The IND provides an exemption from the interstate commerce clause of the Food Drug and Cosmetic Act which bans interstate shipment of unapproved drugs. It is a formal submission with a defined structure and content.[38] At the same time, it can be considered a ''living document'' that is updated by the Sponsor with; for example, protocol amendments, study data, safety reports, manufacturing changes, nonclinical reports, and annual reports. During the development of an IND, it is recommended that sponsors request (a) pre-IND meeting(s) with the FDA to discuss regulatory strategy, study design, manufacturing, study endpoints, and appropriate animal models. Important topics for discussion also should consider how the FDA will decide on whether clinical testing may proceed. The primary focus of clinical evaluation will be on how the Sponsor will ensure the safety and rights of human subjects. The Agency will also look to see that the scientific evaluation of drugs is adequate to permit an evaluation of the drug's evidence of effectiveness and safety. Similarly, pharmacology and toxicology will be evaluated for adequacy of information based on which the sponsor has concluded that it is reasonably safe to conduct the proposed clinical investigations. Manufacturing [chemistry, manufacturing, controls (CMC)] should include sufficient information to assure the proper identification, quality, purity, and strength of the investigational drug.

Animal efficacy studies may be conducted ''when human efficacy studies are not ethical or feasible (6).'' When considering animal efficacy studies, it is important to consult FDA's guidance ''Product development under the Animal Rule.'' When considering an animal model ''more than one animal species expected to react with a response predictive for humans; or one well-characterized animal species model (adequately evaluated for its responsiveness in humans) for predicting the response in humans'' (*6*). The mechanisms of toxicology/pathophysiology should be well understood as well as the effects of the product. This facilitates the Sponsor developing study endpoints that relate to the desired benefit in humans. Finally, the model should be sufficiently reliable such that the Sponsor would be able to predict effective dosing in humans. In the radiation space mice are frequently used, but the literature also supports possible studies in other species, including rats, minipigs, rabbits, dogs, pigs, and NHPs.

One of the most important parts of product development is the regulatory strategy. In brief, the regulatory strategy is the Sponsor's plan for product development with the goal of obtaining regulatory approval. Short-term and long-term plans for the product should be considered, including target label (indication and claims), market and filing options, and competition. A target product profile (TPP) is a helpful tool for developing a regulatory strategy, since it provides a visual of what the product will look like in the end. As you develop the product, the TPP should serve as a goal for guiding the regulatory strategy through early and late development milestones. Therefore it is advisable to reassess and update the TPP and the regulatory strategy as needed to reach an IND filing through to final approval or licensure.

The DAIT ORA mission is to work with DAIT-funded project teams to develop the most efficient regulatory strategy, which anticipates the needs and requirements of health authorities to facilitate the transition of clinical projects from the planning to the operational stage and help to ensure that DAIT-sponsored clinical trials are conducted in compliance with all applicable regulations and requirements to ensure the safety of the patient and the integrity of the trial.

[33] https://www.govinfo.gov/content/pkg/COMPS-8773/pdf/COMPS-8773.pdf.

[34] https://www.loc.gov/item/uscode1964-005021009/.

[35] https://www.fda.gov/regulatory-information/food-and-drug-administration-modernization-act-fdama-1997/fda-backgrounder-fdama.

[36] https://www.fda.gov/regulatory-information/selected-amendments-fdc-act/food-and-drug-administration-amendments-act-fdaaa-2007.

[37] https://www.fda.gov/regulatory-information/selected-amendments-fdc-act/food-and-drug-administration-safety-and-innovation-act-fdasia.

[38] https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.32

Biodosimetry Funding Opportunities with BARDA (R. Wallace)

Although BARDA has been tasked with addressing radiation disasters, they are also involved in the USG response to hurricanes, pandemics, terrorist events, and other natural disasters. BARDA mirrors the development organizations that they support, employing people that have had development experience in a variety of areas, and who provide expertise and advice to current developers. Traditionally, the contract mechanism is used by BARDA to develop products as a public-private partnership. Other innovative programs such as Division of Research, Innovation and Ventures-DRIVe[39] and Early Notification to Act, Control, and Treat (ENACT)[40] are also used to accelerate development of mid-stage products. At BARDA, most funding for biodosimetry starts at a TRL of 3–4, whereas drug development funding typically starts at TRL-6. From 2007–present, BARDA, in its entirety, has had 61 FDA[41] approvals, licensures and clearances, spanning a variety of health threats.

BARDA's biodosimetry program started in 2009, funding 11 technologies in the areas of proteomics, gene expression, and DNA damage. After many tough decisions, quite a few failed technologies, and a $350 million investment, only four candidates remain. These technologies are considered late-stage development and are queued up for Project BioShield[42] funding (special congressional funding for late-stage development and acquisition). However, before the remaining technologies, DxTerity (Duke University/Thermo-Fisher), MRIGlobal, ASELL, Inc. (Meta Systems/Thermo-Fisher), and SRI International (DCN/Gener8/Web Industries), proceed to that step, FDA regulatory clearance or authorization must be obtained. Three of these technologies make use of laboratory instruments already in place within the medical system, but laboratory experts will be needed to run the assays. In contrast, SRI International's POC device is appropriate in a limited resource setting where less-trained personnel can use it.

The Project BioShield 10-year contract structure is common to all awarded projects: pre-EUA (FDA 510(k))/regulatory approval, initial stockpile acquisition, replenishment (if used), and upgrade (if needed) (*65*). To award these contracts, regulatory approval must be obtained. Overall, current Project BioShield-funded technologies can, and should, continue development to obtain faster results, increased accuracy of dose estimate, and improved ease of use. Self-assessment devices are also needed to help the general public determine if they have been exposed or not. Finally, variability needs to be reduced, which may be achieved by assessing radiation injury rather than dose. It is important to remember that a person is being treated, not a dose. While physical dosimetry can be assessed by responders during a radiological/nuclear incident with handheld devices, actual biological implications of a reading can vary from person to person. People have intrinsic genetic variability that will lead to a different biological response to any given radiation dose; therefore, it is important to improve biodosimetry devices to determine the individual health effect or biodose.

Given the circumstances and unpredictable environment with a scare resource setting, tough triage decisions will have to be made. Patients in the expectant category will likely receive only palliative care, so that healthcare providers can focus on the triage of immediate or delayed category casualties and save more lives (*66*). Biodosimetry devices will be critical to this decision making. Beyond determining who is exposed or not, there is also a challenge to distinguish TBI vs. PBI. This uncertainty could make it difficult to determine who should receive treatments like growth factors and/or bone marrow transplants. For this reason, BARDA is moving toward the identification of biomarkers that can help define the level of injury. Regardless of the biodosimetry technology, BARDA continues to seek HT and POC approaches that will likely use established laboratory networks to track results.

SESSION VI: Lessons Learned from the Frontrunners

At the time of writing this manuscript and as discussed above, FDA has licensed four MCMs, but no biodosimetry test has been approved/cleared. During this session, developers of candidate biodosimetry tests and MCMs described their development paths, challenges, and advances in their journey toward U.S. FDA licensure.

Application of the Animal Rule for the Development of Neupogen, Neulasta and Nplate as radiation MCMs (J. Kline)

Amgen has worked closely with USG HHS partners to successfully advance Neupogen, Neulasta, and Nplate as hematopoietic radiation MCMs. The Animal Rule and careful adherence to the considerations laid forth by the guidance played an important role in these successes (*6*).

Neupogen (filgrastim) and Neulasta (pegfilgrastim) are both cytokine growth factors (granulocyte-colony stimulating factors; G-CSF) approved for treatment of H-ARS, with Neulasta being the long-acting form of Neupogen. Originally, Neupogen was approved for several indications, chemotherapy-induced neutropenia (1991), severe chronic neutropenia and bone marrow transplantation (1994), peripheral blood progenitor collection and therapy (1995), and acute myeloid leukemia (1998), while Neulasta was approved for chemotherapy-induced neutropenia (2002). At the time when these two MCMs were reviewed as mitigators of H-ARS by the FDA in 2013, they were approved in over 100 countries, and were part of 26,421

[39] https://drive.hhs.gov/.
[40] https://drive.hhs.gov/enact.html.
[41] https://www.medicalcountermeasures.gov/barda/fdaapprovals/.
[42] https://www.phe.gov/about/barda/Pages/Project-Bioshield.aspx.

(8.8M individuals) and 5,419 (4.4M individuals) clinical trials for Neupogen and Neulasta, respectively. Therefore, their tolerability profiles were well-understood.

Understanding the mechanism of action of these drugs and the natural history of disease postirradiation was critical. Data collection from animal studies and human data from radiation incidents such as Hiroshima, Nagasaki, and Chernobyl demonstrated that increasing radiation dose resulted in increased mortality. After the Nagasaki incident, the LD_{50} for humans was estimated to be 4.4 Gy, while the $LD_{50/60}$ after the Chernobyl accident was thought to be ~8.8 Gy, and the $LD_{50/60}$ for NHP was found to be ~7.5 Gy (*11*). Mortality is preceded by depletion of terminally differentiated immune cells, with severe neutropenia (<0.1 neutrophils $\times 10^3$ cells/μL) occurring at around 9–12 days postirradiation in NHPs (*11, 67, 68*). These findings showed that neutrophils are critical to fight infections, and infection accompanied by neutropenia is associated with significant morbidity and mortality after irradiation.

With a well-understood mechanism of action, where Neupogen and Neulasta act on hematopoietic progenitor cells to accelerate neutrophil production and recovery, impacting the mitotic and post-mitotic phases (*69, 70*) both drugs were poised for MCM development. The safety profile was also well understood and additional radiation safety studies were conducted in mice, dogs, minipigs and NHPs exposed to sublethal or lethal doses of radiation, demonstrating the safety of use for the H-ARS indication. In the pivotal studies carried out to support licensure, NHPs were exposed to a mid-lethal dose of 7.50 Gy [$LD_{50/60}$] of linear accelerator (LINAC) photon irradiation, and Neupogen (10 μg/kg/d) was administered 1-day post-TBI and continued daily until the absolute neutrophil count (ANC) was >1,000/μL for 3 consecutive days. Neupogen treated groups demonstrated higher survival compared to the vehicle-treated cohort ($p = 0.023$), and the duration of neutropenia was also significantly reduced (*71*). Similarly, Neulasta demonstrated efficacy in irradiated mice and NHPs. NHP were exposed to 7.5 Gy TBI and administered Neulasta (300 μg/kg) on days 1 and 8 postirradiation. Treatment resulted in a 91% survival in the Neulasta-treated group compared to 48% survival in the control group ($p = 0.0014$), and also decreased the median duration of neutropenia (*72*). The study endpoints in these pivotal experiments were clearly related to the desired benefit in humans -i.e., survival, and decrease in duration of grade 3 and grade 4 neutropenia.

Selection of dose in humans-population modeling. Based on the neutrophil data from irradiated NHP, and clinical data from adult and pediatric patients undergoing chemotherapy, a mechanism-based PK/PD model was used to quantify the relationship between ANC profiles and overall survival after filgrastim or pegfilgrastim administration in NHPs (in the H-ARS setting). This information was also used to predict the effect of radiation exposure and filgrastim or pegfilgrastim treatment on ANC profiles after radiation exposure and overall survival in humans (adults and pediatric patients) in a similar setting.

Regulatory advanced development timeline. The Animal Rule was established in 2002, and Amgen had its first pre-IND meeting for Neupogen as a H-ARS MCM in 2005. NIAID, as HHS partners, filed a pre-IND and development plans in 2006. In 2011, NIAID filed the final study reports of NHP animal model development and Neupogen efficacy. This led to convening of a U.S. FDA advisory committee meeting in 2013 (discussed below). These discussions between Amgen, FDA and NIAID laid the groundwork for the pathway to regulatory approval for these MCMs. Based on the survival data and PK/PD modeling, Amgen submitted a supplemental BLA for Neupogen in 2014, and one for Neulasta later that year, resulting in approvals March and November of 2015, respectively.

Challenges in the regulatory pathway. Although the Animal Rule was authorized in 2002, only 5 approvals were granted this way from 2002–2014, and none of them were for radiation MCMs. The path to approval of Neupogen required frequent interactions with the FDA to obtain clarity regarding the animal models to study H-ARS. Modeling studies were needed to translate data from NHPs to human dose. Since Amgen was the first company seeking approval of a drug for the radiation indication, the approval process was the subject of a joint meeting of the FDA Medical Imaging Drugs Advisory Committee and the Oncologic Drugs Advisory Committee, held May 3, 2013.[43] The committee was tasked with thoroughly vetting the models and the proposed development path to ensure that there was agreement between the animal data and its applicability to humans. The voting question for the Advisory committee was, ''Considering the known filgrastim effects in the chemotherapy setting, the NIAID study data, and assuming filgrastim would be administered in a clinical dose regimen similar to that evaluated in the NIAID study, is filgrastim therapy reasonably likely to produce clinical benefits in humans exposed to radiation that is likely to induce myelosuppression during or after a radiological/nuclear incident?'' The final vote was 17 in favor and 1 opposed.

Nplate (Romiplostim) approved as a radiation MCM. Although this advancement was made after the meeting described herein, it is included to provide an up-to-date accounting of available MCMs for H-ARS. Nplate was initially approved in 2008 for treatment of patients with chronic immune thrombocytopenia.[44] Romiplostim is a thrombopoietin (TPO) receptor agonist designed to bind the TPO receptor (c-Mpl) and stimulate megakaryocyte-mediated production of platelets. The peptide-containing domain is specifically designed to activate the receptor, but avoid the development of antibodies that cross-react to

[43] https://wayback.archive-it.org/7993/20170403223953/https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/MedicalImagingDrugsAdvisoryCommittee/ucm334176.htm.

[44] https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/125268s0026lbl.pdf.

endogenous TPO (*73*). As with neutropenia, it is understood that duration of thrombocytopenia is linked to mortality in irradiated subjects, and it was hypothesized that reducing thrombocytopenia could increase survival in subjects exposed to myelosuppressive doses of radiation (*74*). The mechanism of action of romiplostim is reasonably well-understood, and a single subcutaneous injection of romiplostim shows a dose-dependent increase in platelet counts 4–9 days post-dose in humans, with the platelet peak appearing on days 12–16 after drug administration (*75*). Romiplostim also demonstrated survival efficacy and platelet recovery in two irradiated animal species - C57BL/6 mice and NHPs (*76*). At the time that the workshop was conducted, pivotal NHP survival studies and selection of drug dose to humans were still on-going. Both NHP and dose-translation studies (*77*) were successfully completed, and the U.S. FDA approved Nplate as a radiation MCM in January, 2021.[45]

Regulatory Perspective on Developing a Point-of-Care (POC) Triage Radiation Biodosimeter (M. Greenstein)

SRI initially received BARDA funding in 2010 to develop a POC radiation biodosimeter for triage. The SRI device provides a positive/negative qualitative answer based on a qualitative proteomic measurement. BARDA funded the early biomarker discovery stage with mass spectrometry to identify putative panels and targets. Subsequently, SRI developed an optimal biomarker panel using irradiated NHP and clinical samples (*78*). Biomarker selection was further impacted by differences in the kinetics of the selected panel that is required to be consistent over 7 days postirradiation, however not all the biomarkers in the panel have the same time-course trajectory. As described above, BARDA requested technologies with the capability to respond to a 10 kT nuclear event in a major U.S. city, resulting in the potential exposure of 1M individuals to prompt irradiation (fallout is not factored into this scenario). SRI was tasked with producing a clinical laboratory improvement amendment (CLIA)-waived POC device that utilizes capillary blood samples to triage 1M individuals over 6 days postirradiation (~167,000 tests/day). Targeting a cut-off of 2 Gy, if the patient's sample results in a readout of <2 Gy, he/she is tagged as negative and sent home with instructions. Those with a result of >2 Gy are tagged as positive and require a quantitative assay to identify the amount of radiation exposure, and further medical intervention. This rapid triaging constitutes an enormous logistical challenge especially when combined injuries such as broken bones, trauma, and bleeding are factor in. Effective triage requires a low FPR, but sensitivity requires a low FNR. To that end, SRI has consistently tried to find the balance between the two.

SRI technical development process. The workflow consists of a capillary blood collection with a dedicated collection tube. The drop of blood is placed into a cartridge that uses a lateral flow assay, and the analyzer is designed to be CLIA-waivable and amenable to a mass casualty situation. The assay quantifies the levels of target protein AMY1, FLT3L, and MCP1 concentrations. The data are analyzed by a statistical classification algorithm that was designed to be species independent. The test statistics (TS) is calculated as a sum of the three protein concentrations for an individual measurement. A large number of well-controlled, normal population indices were measured to build a population distribution. The TS threshold to determine qualitative result is set based on several verification studies with both irradiated NHP and from radiotherapy patients. The individual is negative if TS$<$TS threshold, or positive if TS$>$TS threshold.

The system components consist of POC analyzer, sample collector and a lateral flow assay cartridge. The POC analyzer has a shelf life of 10 years, is designed as CLIA-waivable and equipped with global positioning and wi-fi capabilities, and can run on AA batteries, a 12V car battery or a 110V supply. The consumable components are the sample collector and lateral flow assay cartridge, each with a 2-year shelf life due to the collection buffer and assay reagents.

Percentile Classification Algorithm. After TBI with radiation doses of 0, 2, 4, 6 and 8 Gy, the density of test statistics for NHPs was plotted against radiation dose to show the population distribution vs. test statistics. Because of the biology and broadness of distribution of the protein concentrations, at the cutoff between negative samples and the 4 Gy group in NHP, there is some degree of overlap contributing to the FPR and FNR values (*79*). It is acknowledged that in the end, there is a tradeoff between these two values. Human data from Stanford University (*80*) were used to generate a dose table for both NHP and humans and classic imprecision curves for NHP and humans were built. At the 4 Gy cut-off in NHPs, the biomarkers give a 95% positive result; however, the human imprecision curves had far sparser radiation doses, and patients receiving 2 Gy of radiation also receive concurrent chemotherapy, complicating the establishment of dose equivalents. Currently, SRI is performing analytical validation, using spiked venous blood,[46] supplemental NHP validation, which will include fractionated irradiation protocols to compare to human fractionated irradiation, and clinical validation in which reference ranges for the protein concentrations potential confounding conditions will be established, and the numbers of TBI patients receiving fractionated radiotherapy will be expanded.

SRI's regulatory interactions. SRI has had extensive interactions with the FDA regarding their POC triage biodosimeter. In 2014, SRI had an introductory pre-

[45] https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/125268s167lbl.pdf.

[46] https://www.fda.gov/media/71075/download.

submission meeting with the FDA and provided information on the preliminary panel, statistical methods, and NHP data. In 2016, SRI provided the FDA with feasibility plans; in 2018, they submitted verification plans; and in 2019, they requested FDA comments on their validation protocols. Altogether, FDA pre-submission meetings have proven to be extremely useful in gaining clarity on FDA's expectations.

Challenges of advanced development of the SRI POC triage biodosimetry test include the lack of an intended use population, partially abrogated by using NHPs and cancer patients receiving TBI, and the challenge in translating these results to a reliable cut-off point (2 Gy) for separating those needing treatment from the ''worried well.''

The SRI POC radiation biodosimetry instrument is not a typical medical device. The intended use of the device sets the balance between the FPR/FNR optimization choices. Given the lack of the intended use population, development relies heavily on NHP models. The composite validation strategy requires NHP to human dose equivalence assumptions, and an integral component to that strategy is a species-independent classifier. Despite these drawbacks, work continues on these and other approaches, because if no triage device is available, the medical radiation response will not be able to handle the anticipated patient numbers.

CONCLUSION

The ability of the USG to respond to a radiological and/or nuclear incident is contingent upon availability of suitable devices to triage, and MCMs to treat affected populations. The process of translating basic discoveries to clinical use and ultimately to improve public health is critical for preparedness but is fraught with challenges at pre-clinical and clinical research levels. NIH policies and FDA guidance provide pathways that can inform drug and device developers in the continuum of research translation, with the objective of FDA approval/clearance and implementation. Despite decades of efforts, it is clear that much work is needed to adequately prepare the nation to meet the challenges of an unanticipated radiological/nuclear mass casualty event. Patients that survive the hematopoietic radiation dose, might eventually experience DEARE, and currently no MCMs are approved for any DEARE outcome. Given that no biodosimetry device has been cleared by the FDA, there is an urgent need to accelerate this field such that in the event of a disaster, triaging the exposed population from the ''worried-well'' can aid disaster response in a scare resource environment. NIAID and BARDA, along with other government agencies, will continue to work together with academic and corporate partners to achieve the critical public health emergency need for rapid biodosimetry tests as well as safe and effective radiation countermeasures to address the multiorgan sequalae observed after radiation exposure during a radiological or nuclear incident. Further, communications with the global radiation research community (International Commission on Radiological Protection,[47] World Health Organization,[48] Running the European Network of Biological and Retrospective Physical Dosimetry)[49] can enhance exchange of novel ideas and approaches and advance the state of the science for the radiation community.

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[47] https://www.icrp.org/.
[48] https://www.who.int/health-topics/radiation#tab=tab_1.
[49] https://www.reneb.net/.

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