NIH Policies and Regulatory Pathways for the Advancement of Radiation Medical Countermeasures and Biodosimetry Tools to U.S. FDA Licensure

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COMMENTARY

NIH Policies and Regulatory Pathways for the Advancement of Radiation Medical Countermeasures and Biodosimetry Tools to U.S. FDA Licensure

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INTRODUCTION

The Radiation and Nuclear Countermeasures Program (RNCP), which is part of the National Institute of Allergy and Infectious Diseases (NIAID), within the National Institutes of Health (NIH) sponsored a workshop on ''Policies and Regulatory Pathways to Food and Drug Administration (FDA) Licensure: Radiation Countermeasures and Biodosimetry Devices'' that was held on October 9–10, 2018, in Bethesda, MD. This meeting was attended by U.S. Government (USG), academic, and industry researchers involved in the development of radiation medical countermeasures (MCMs) and biodosimetry tools. The objectives of this meeting were to: 1. discuss current policies and regulatory pathways to aid in the advancement of radiation MCM and biodosimetry tools, 2. identify resources, guidance, and gaps in research practices and existing policies, and 3. provide a platform for an open and informal dialogue among scientists and government partners with expertise in MCM or biodosimetry development. Discussion topics centered on: 1. defining the context for deployment of MCMs and biodosimetry platforms, 2. animal models of irradiation developed in response to the FDA Animal Rule and Biodosimetry Guidance (1), 3. NIH policy and support for MCM development and biodosimetry advancement, and 4. lessons learned from industry frontrunners. More detailed information can be found in the full meeting report available online (https://doi.org/10.1667/RADE-21-00157.1)

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DEFINING THE CONTEXT FOR DEPLOYMENT OF MCMS AND BIODOSIMETRY PLATFORMS

After a nuclear incident, the USG response relies on scenario modeling at the federal, state, and local level. Responders will likely be resource-limited; therefore, to address screening needs during a radiation public health emergency, a USG interagency working group developed the radiation-specific TRiage, TReatment, TRansport (RTR) system (2). This effort is designed to optimize resource allocation (material and personnel) to the most appropriate staging zones. Inherent to this planning is the need to provide continuous monitoring. Triage will direct scarce resources to those individuals who will benefit the most from medical care, whereas others will be released for observation or provided palliative care, depending on the severity of the exposure. If more help is needed at the local level, a federally sponsored National Disaster Medical System (NDMS) is available. The NDMS deploys personnel and augments the local response and health care systems with Veterans Administration hospitals and hospitals within the NDMS network, including the Radiation Injury Treatment Network (RITN) (3). Any response to a nuclear disaster will require a large and coordinated effort by local responders and providers, up to and including regional and national receivers, to care for patients.

ANIMAL MODELS TO SUPPORT RADIATION MCM DEVELOPMENT

Animal models. Animal models serve as surrogates in situations where it is not ethical to conduct human studies, as is the case for radiation studies. The animal models selected should model the disease of interest, and a drug's anticipated mechanism of action. Studies must be adequate

and well-controlled, and the effect of the challenge agent in the laboratory model should be predictive of the human condition. For drug and biological product MCM development, the US FDA Animal Rule (AR) guidance should be followed (21 CFR 314.610(a) for drugs, and 21 CFR 601.91(a) for biological products) (4). Given the complexity of the AR, developers are encouraged to consult early and often with the US FDA to ensure that the critical path selected to move an approach forward is acceptable to the agency.

Many small animal (e.g., mouse, rat, guinea pig) models of radiation are detailed in the literature, which include: total-body irradiation (TBI) for hematopoietic acute radiation syndrome (H-ARS) (5), and gastrointestinal (GI)-ARS (6); partial-body irradiation (PBI) for GI-ARS and lung injuries (7); whole thorax lung irradiation (WTLI) exposure for lung effects (8); and PBI for renal and other delayed effects of acute radiation exposure (DEARE) (9). Large animal models [e.g., nonhuman primate (NHP), minipig (MP), full-size pig (Yorkshire Swine), or canine] have also been developed for TBI H-ARS (10) or GI-ARS (6), PBI GI-ARS (11, 12), WTLI for lung (13), TBI kidney[2] (14), and cutaneous radiation injury (CRI) (15). Since large animal resources are limited and costly, preliminary efficacy and dosing studies should be completed in small animal studies. The adequate design of preclinical studies is critical as this research feeds into more advanced development funded either by NIAID/RNCP or the Biomedical Advanced Research and Development Authority (BARDA).

Advanced product development. BARDA incorporates flexible authorities, such as multi-year support, promotion of innovation, industry partnerships, and cutting-edge expertise to develop MCMs and biodosimetry tools for radiation injury. To date, BARDA's Project BioShield (16) has supported 27 radiation products; of which eight products advanced to the U.S. FDA for approval/licensure/clearance, and fourteen were acquired for the Strategic National Stockpile (SNS). Stockpiled agents include ThyroShield® (potassium iodide oral solution), calcium- and zinc-diethylenetriamine penta-acetic acid (DTPA), Neupogen®, Neulasta®, and Leukine®.[3] BARDA also supports a robust radiation biodosimetry portfolio, which includes point of care (POC) triage screening tests to discern individuals needing medical evaluations from those who can evacuate, as well as high throughput laboratory tests, which more accurately report individual absorbed radiation dose, and inform medical care. BARDA is also working on the development of thermal burn products, since combined radiation injuries are expected (17). Developing biodosimetry tools is challenging since regulatory strategies are still being developed. Nonetheless, BARDA has advanced four of these products into validation and clinical testing, with one pre-Emergency Use Authorization (EUA) data package filed.[4] The end goal is to obtain U.S. FDA-cleared triage tools to help separate concerned citizens from individuals with medically significant radiation doses, and to assist physicians in determining who requires administration of life-saving treatments.

NIH POLICY AND FDA REGULATORY GUIDANCE

NIH policy to enhance reproducibility through rigor and transparency. 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 that end-users receive 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, and the potential for adverse events (i.e., side-effects or failure modes) should be understood and controlled, if possible. The concept of quality should be incorporated into every facet of drug and device development, from research through clinical trials and post-marketing surveillance. Investigators are responsible for managing key resources that are tantamount to improving rigor and transparency. The NIH Office of Extramural Research provides policy guidelines for Rigor and Reproducibility.[5] Additionally, NIH training modules are available.[6]

Radiation biodosimetry development and validation challenges: a regulatory perspective. Radiation biodosimetry devices are a subset of in vitro diagnostics (IVDs) that can be used to estimate the absorbed radiation dose received by individuals (18). Use of these IVDs can range from field triage settings (POC) to confirmatory testing and clinical evaluation (high throughput). The regulatory path to market and identification of pivotal validation studies that need to be conducted can be a challenge. Some instruments, including biodosimetry devices, may qualify for an EUA. The EUA permits the 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 Federal Food, Drug, and Cosmetic Act.[7] Requests for EUAs go to the FDA Office of the Commissioner; however,

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

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

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

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

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

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

the path had been somewhat obscure until the recent EUAs issued for COVID-19 diagnostic tests. To determine the best path forward, developers should refer to the available FDA guidance document, ''Radiation Biodosimetry Medical Countermeasure Devices Guidance for Industry and Food and Drug Administration Staff'' (1). For a successful IVD development project, the FDA recommends early and frequent interactions, careful consideration of the path to market, attention to special controls for *De Novo* submissions, and preparation of a pre-EUA submission.

Development of therapeutics for radiological and nuclear emergencies. If an approved/licensed drug is being repurposed as an MCM, an extensive safety profile in humans will likely already be available through clinical experience and post-marketing studies. If not, a traditional Investigational New Drug (IND) application will be required to conduct Phase 1 studies in healthy volunteers with appropriate age, sex and race considerations. As with all drug development, preclinical safety and toxicology studies will also need to be addressed in animal models. MCM products may be eligible for fast-track, priority review, or breakthrough therapy programs, which can considerably reduce the review time for approval or licensure. Orphan product designations and grant programs are also available for indications that affect less than 200,000 patients per year in the U.S. Finally, in the absence of adequate, approved, and available alternatives, an EUA can also be used for unapproved products or indications for use in public health emergencies.

GOVERNMENT SUPPORT FOR ADVANCEMENT OF MCMS AND BIODOSIMETRY TECHNOLOGIES

The mission of the NIAID/RNCP program is to support early through late-stage research to develop radiation/nuclear MCMs and biodosimetry tools (19). NIAID/RNCP has funded the development of rodent and NHP models of H-and GI-ARS (7, 20, 21). In addition, animal models for DEARE continue to be developed for GI and lung injury (22, 23). Rat and canine models have also been established to test radionuclide decorporation agents (24, 25). NIAID/RNCP efforts have directly led to three INDs for oral decorporation agents and a cellular MCM, the manufacture or reformulation of three MCMs, and the FDA approval of three MCMs for H-ARS – Neupogen and Neulasta (2015), and Nplate® (2021). In 2018, BARDA-funded studies led to the FDA approval of Leukine (sargramostim) for H-ARS. The NIAID/RNCP also helps advance biodosimetry tools by providing valuable NHP biological samples to developers for proof of principle analysis (26–29). This pipeline is fueled by a company engagement pathway that begins with an introductory teleconference with NIAID, followed by a Radiation and Nuclear Group – Advanced Product Development (RNG-APD) interagency meeting, with participation from several government partners and testing facilities. The RNG-APD allows for early-stage feedback and establishes the best drug development pathway for the product.

BARDA also employs subject matter experts who have experience in a variety of areas in product development. Generally, contracts are used to develop products as a public-private partnership. Other innovative programs such as the Division of Research, Innovation, and Ventures (DRIVe)[8] and Early Notification to Act, Control and Treat (ENACT)[9] are also used to accelerate the development of products. From 2007–2020, BARDA, in its entirety, has had over 59 FDA approvals, licensures, and clearances spanning a variety of health threats.[10] BARDA's biodosimetry program started in 2009 with the funding of 11 technologies in the areas of proteomics, gene expression, and DNA damage.

LESSONS LEARNED FROM THE FRONTRUNNERS

The FDA has approved four MCMs to date for H-ARS, but no biodosimetry test or device has been cleared as of the time of this publication. Therefore, lessons learned from developers of candidate MCMs and biodosimetry tools, including challenges and advances in their journey toward U.S. FDA licensure, can be informative for other researchers.

Application of the FDA Animal Rule for the development of Neupogen, Neulasta, and Nplate as radiation MCMs. Amgen worked closely with USG partners to successfully advance Neupogen, Neulasta, and Nplate as hematopoietic radiation MCMs. Careful adherence to the considerations laid forth by the AR guidance played an important role in these successes (4). Prior to their consideration for H-ARS, these drugs were approved for medical use in over 100 countries and were part of large clinical trials; with 26,421 (8.8 M individuals) and 5,419 (4.4 M individuals) clinical trials for Neupogen and Neulasta, respectively. Therefore, the extensive medical use and well-understood tolerability profiles of these drugs also played a role in their success.

To support the radiation indication, pivotal studies were conducted in mice and NHPs. NHPs were exposed to a lethal dose of 7.5 Gy [$LD_{50/60}$] of linear accelerator (LINAC) photon irradiation. Neupogen (administered daily, starting at 24 h postirradiation)-treated groups demonstrated higher survival compared to the vehicle-treated cohort, and duration of neutropenia was also significantly reduced (30). Similarly, Neulasta demonstrated efficacy in irradiated mice and NHPs exposed to 7.5 Gy TBI. Neulasta treatment resulted in a 91% survival as compared to 48% survival in the control group, and also decreased the median duration of neutropenia (31).

Although the FDA approval of romiplostim (Nplate) 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 the

[8] https://drive.hhs.gov/.
[9] https://drive.hhs.gov/enact.html.
[10] https://www.medicalcountermeasures.gov/barda/fdaapprovals/.

treatment of patients with chronic immune thrombocytopenia,[11] and the mechanism of action of the drug is well-understood. A single subcutaneous injection of romiplostim shows a dose-dependent increase in platelet counts, with a platelet peak appearing on days 12–16 after dosing in humans (32). Romiplostim also demonstrated improvements in survival and platelet recovery in two irradiated animal species, C57BL/6 mice (33) and NHPs (34). At the time of the 2018 workshop, pivotal NHP survival studies and the selection of the human dose were still ongoing. Since the workshop, NHP and dose-translation studies (35) were completed, and in January 2021 the FDA approved Nplate as a radiation MCM.[12]

Regulatory Timeline for Advanced MCM Development.

- 2002 FDA Animal Rule was established.
- 2005 Amgen had its first pre-IND meeting for Neupogen as a H-ARS MCM.
- 2006 NIAID, as HHS partners, filed pre-IND and development plans.
- 2011 NIAID filed the final study reports of Neupogen NHP animal model development and efficacy.
- 2013 US FDA Advisory Committee met to discuss groundwork for an eventual regulatory pathway to approval, following discussions between Amgen, FDA, and NIAID.[13]
- 2014 Amgen submitted a supplemental BLA for Neupogen based on the survival data and PK/PD modeling.
- 2015 FDA approved Neupogen and Neulasta in March and November, respectively.
- 2018 FDA approved Leukine for H-ARS, based on BARDA-funded studies.
- 2021 FDA approved Nplate in January.

Regulatory perspective on developing a POC triage radiation biodosimeter. In 2010, SRI International received BARDA funding to develop a Clinical Laboratory Improvement Amendments (CLIA)-waived POC biodosimeter device that utilizes capillary blood samples capable of triaging up to one million individuals over 6 days after exposure (~167,000 tests/day). The goal was to distinguish concerned citizens in good health but believe to have been exposed (<2 Gy), from people exposed to a high radiation dose (>2 Gy) that likely require medical intervention. The assay involves the use of a capillary blood collection. The drop of blood is placed into a cartridge that uses a lateral flow assay and is amenable to a mass casualty scenario. The assay quantifies the levels of the AMY1, FLT3L and MCP1 target protein concentrations.

SRI's regulatory interactions. SRI had an introductory pre-submission meeting with the FDA, and provided information on their preliminary panel, statistical methods, and NHP data (2014). Since the first meeting, SRI has submitted feasibility plans (2016), verification plans (2018), and requested FDA comments on their validation protocols (2019). Altogether, FDA pre-submission meetings have proven to be extremely useful in gaining clarity on FDA's expectations. Development challenges for 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 of translating these results to a reliable cut-off point (2 Gy) needed for triage. Although the development path is unclear, the government-industry partnership continues to forge ahead to ensure availability of a reliable triage device for use during a radiological or nuclear incident.

CONCLUSION

The ability of the USG to respond to a radiological and/or nuclear incident is contingent upon the availability of suitable tools to triage, and MCMs to treat affected populations. 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 licensure/approval/clearance and implementation. Regardless, the process of translating basic discoveries to clinical use to improve public health is fraught with challenges at pre-clinical and clinical research levels. This meeting provided an open informal dialogue between key stakeholders, product developers and government partners, with expertise in MCM or biodosimetry development. Available resources, guidance, and gaps in research practices and existing policies were discussed. USG agencies will continue to work with academic and corporate partners to overcome these challenges, to obtain effective MCMs and rapid biodosimetry tests to effectively manage a radiological or nuclear incident.

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

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

[13] https://www.fda.gov/advisory-committees/human-drug-advisory-committees/medical-imaging-drugs-advisory-committee. Please select the live link, ''FDA Archive.''

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