Scientific research and product development in the United States to address injuries from a radiation public health emergency

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ABSTRACT

The USA has experienced one large-scale nuclear incident in its history. Lessons learned during the Three-Mile Island nuclear accident provided government planners with insight into property damage resulting from a low-level release of radiation, and an awareness concerning how to prepare for future occurrences. However, if there is an incident resulting from detonation of an improvised nuclear device or state-sponsored device/weapon, resulting casualties and the need for medical treatment could overwhelm the nation’s public health system. After the Cold War ended, government investments in radiation preparedness declined; however, the attacks on 9/11 led to re-establishment of research programs to plan for the possibility of a nuclear incident. Funding began in earnest in 2004, to address unmet research needs for radiation biomarkers, devices and products to triage and treat potentially large numbers of injured civilians. There are many biodosimetry approaches and medical countermeasures (MCMs) under study and in advanced development, including those to address radiation-induced injuries to organ systems including bone marrow, the gastrointestinal (GI) tract, lungs, skin, vasculature and kidneys. Biomarkers of interest in determining level of radiation exposure and susceptibility of injury include cytogenetic changes, ’omics’ technologies and other approaches. Four drugs have been approved by the US Food and Drug Administration (FDA) for the treatment of acute radiation syndrome (ARS), with other licensures being sought; however, there are still no cleared devices to identify radiation-exposed individuals in need of treatment. Although many breakthroughs have been made in the efforts to expand availability of medical products, there is still work to be done.

Keywords: radiation; preparedness; medical countermeasures; US government; radionuclides; biodosimetry

INTRODUCTION

This article presents an overview of the US Government’s efforts to expand scientific research, to ensure medical preparedness to address civilian casualties in the wake of a radiation public health emergency. Given the ever-present threat of a large scale radiation public health emergency, it is critical that advanced planning be carried out, and strategic investments be made into research to better understand the impact of radiation on the body, and how to diagnose, mitigate and treat any resulting injuries. For the purposes of this manuscript, the assumed scenario is a mass casualty radiological or nuclear incident, as opposed to a small-scale industrial accident (which would likely entail more personalized patient care provided quickly post-event). In addition, the focus is on the scientific research that is being carried out behind the scenes, as opposed to a consideration of the logistics (e.g. planning and coordination of response partners). There are a number of US agencies that are involved in the development of medical countermeasures (MCMs) to treat radiation injuries, and identification of biomarkers of radiation exposure that can be used for triage and to guide patient treatment. Although funding for this development is spread across several agencies, the bulk of the support for early through late-stage research and development is carried out within the US Department of Health and Human Services (HHS) [1]. Much of the early research on mechanisms of radiation injury and identification of targets for MCM development is supported by the Radiation and Nuclear Countermeasures Program (RNCP), in the National Institute of Allergy and Infectious Diseases (NIAID), a part of the National Institutes of Health (NIH) [2–4]. RNCP activities also include late-stage development; however, the majority of these approaches often fall to the Biomedical...
Advanced Research and Development Authority (BARDA), within the Office of the Assistant Secretary for Preparedness and Response (ASPR), at HHS. Other agencies that have similar missions, including parts of the Department of Defense (DoD) and the National Aeronautics and Space Administration (NASA), also fund work on different aspects of radiation injury, leveraging and complementing the work done through HHS. The focus of this manuscript is on US-funded scientific research to enhance radiation medical preparedness, and was the emphasis of the presentation on which this review is based (the 66th Annual Meeting of the Radiation Research Society, 2020).

Fortunately, the history of radiation incidents on US soil have been few in terms of large-scale exposures; however, there have been more than 50 confirmed nuclear reactor accidents in the US that involved either loss of life or significant property damage. Perhaps the most well-known was that of Three-Mile Island in 1979 [5]. This accident involved a partial meltdown of one of the reactors, which resulted in the release of radioactive gases and iodine into the environment. No immediate fatalities were reported, and epidemiological studies have not identified a definitive link between the accident and cancer incidence in the area [6, 7]. Nonetheless, the cleanup costs were exorbitant. There have also been a handful of criticality events, with seven deaths reported—the most recently reported fatality from these was in 1964 [8]—as well as radiation therapy over-exposures and small-scale industrial/medical incidents involving lost/stolen radiation sources, but the possibility of a coordinated nuclear attack involving a rogue element continues to be a concern.

**DISCUSSION**

**US radiation emergency medical preparedness**

The events that unfolded on 9/11 truly galvanized the USA to reconsider its emergency medical response posture. Because investments in radiation medical research and deterrence had largely ceased after the end of the Cold War in the early 1990s, it was necessary to find a way to bring these programs back into being, while assessing what medical products might be required from a planning perspective. It became clear that a mass casualty event would necessitate rapid and accurate triaging of potentially-exposed individuals, due to the fact that resources would likely be constrained during a mass casualty incident (Fig. 1) [9]. To address these shortcomings, HHS sought to develop medical response plans, which included consideration of a number of radiation exposure scenarios [10]:

- Detonation of a nuclear bomb or improvised nuclear device
- Nuclear power plant accident or attack
- Dissemination of radionuclides
  - Dirty bomb or other dispersal device
  - Hidden radiation-emitting source
  - Radionuclide release in air, water, food supply

Perhaps the most frightening possibility is the detonation of a large nuclear device, which could result in many casualties suffering burns, wounds and fractures, as well as exposure to potentially large doses of radiation from the prompt blast or resulting fallout [11]. Other situations of concern include radionuclide dispersals or the placement of devices that emit radiation in public locations [12]. The concept of operations (CONOPS) that have been worked out by the US Government suggest that it will be very difficult to get necessary triage devices and treatments to where they are needed in a time frame earlier than one day [13]. This assumes a mass casualty incident, as it may be possible to mount a prompter response to a smaller-scale exposure, such as an industrial or criticality accident. For this reason, most of the biodosimetry and MCMs development for civilians has assumed triage or product administration at 24 hours or later after the incident. Carrying out the 2004 HHS mandate to support research and development of triage tools and treatments for radiation injuries led to the formation of the Public Health Emergency Medical Countermeasures Enterprise (PHEMCE) (Fig. 2) [14].

This organizing structure has enabled different agencies within HHS, such as the US Food and Drug Administration (FDA), the ASPR, BARDA, the Centers for Disease Control and Prevention (CDC) and the NIH, to work together in the different response areas of civilian preparedness. In addition, HHS coordinates with other parts of the US Government, including the DoD and NASA, whose missions often overlap with those of HHS. For example, the DoD has investments in radiation, but as they are tasked to address troop casualties, their requirements are different than for civilian populations. A majority of the DoD’s funding for radiation research is provided to the Armed Forces Radiobiology Research Institute (AFRRI), where researchers, who are also supported by NIAID and BARDA, carry out important work on mechanisms of radiation injury, development of treatments and exploration of radiation-specific biomarkers of damage [15]. Similarly, the NASA Human Research Program [16] has a primary goal of protecting astronauts from high energy radiation exposures in space, which often involves ground-based studies that have relevance for advancing MCM approaches of interest to the HHS.

**Global preparedness**

In addition to US preparedness for a radiological or nuclear incident, governments across the globe are developing plans for use during and following a radiation mass casualty incident. Although focused more on incident preparedness, as opposed to novel scientific research, organizations like the World Health Organization Radiation Emergency Medical Preparedness and Assistance Network (WHO-REMPAN) [17], and the North Atlantic Treaty Organization (NATO), have done tremendous work in planning for medical aspects of a military response [18]. In addition, physicians and researchers from France [19-21], Russia [22, 23], and other countries such as those in South America [24-26] and Japan (Tokaimura [27, 28] and Fukushima [29-33]) have had interactions with individuals and groups injured by radiation exposure (primarily from industrial or nuclear power plant accidents). Working often with the International Atomic Energy Agency (IAEA) to share these experiences and lessons learned, these unfortunate incidents have helped to guide both planning and research for medical preparedness. NATO has also funded work to develop biomarker tools [34] and has held multiple meetings to explore the use of the MEdical TReatment Protocols (METREPOL) system [35] and SEARCH database [36] to predict radiation health outcomes based on clinical signs and symptoms [37]. NATO task forces have explored radiation risk communication [38], and NATO tabletop exercises in a variety of areas [39-43], such as assessing injuries, conducting surveys and radiological sampling, consideration of vulnerable populations, and estimating health risks, have been key to understanding best practices in the wake of a radiation emergency. Finally, the TMT Handbook, published by the Norwegian Radiation Protection Authority in 2009,
Fig. 1. Triage categories for radiation medical response according to resource availability [9].

Fig. 2. Public Health Emergency Medical Countermeasures Enterprise (PHEMCE) agency lead roles (adapted from https://www.phe.gov/Preparedness/mcm/phemce/Pages/mission.aspx).

contains important information on actions that need to be taken in the immediate aftermath of a radiological or nuclear emergency, including communication, decontamination, dose assessment, transportation and early medical management [44]. Similar activities have also been described for the USA [45].

Radiation medical product development research
Following recommendations of a blue ribbon panel that was convened in 2004, the NIAID RNCP established research in three main areas [10]. Topics included development of products to mitigate and treat radiation injuries, to remove internalized radionuclides from the body, and advancement of biomarkers and devices to assess the severity of an individual’s radiation exposure reliably and quickly. This triage piece is crucial to guide healthcare professionals on how to best address medical interventions for large groups of potentially-exposed people. When the program was initiated in 2004, there was also a need to provide funding to develop basic infrastructure, including the establishment of facilities that could be used to irradiate small and large animals, development of models of radiation exposure, support for training and educational programs and a means to interface with industry. This has been accomplished by close partnering with other HHS and non-HHS agencies, to ensure promising approaches continue along the critical path of translational research.

To address the primary interest areas, the RNCP portfolio has been developed to identify MCMs to treat injuries to the different organ systems that are known to be involved in radiation damage, including acute responding tissues like bone marrow, the gastrointestinal (GI) tract, skin and vasculature, as well as those arising at later times.
post-irradiation, including the lungs, kidneys, heart and brain. Injuries involving radiation combined with other trauma, for example, burn, wound or infection, have also represented an area of dedicated funding. Rounding out these focus topics is the search for biomarkers of radiation exposure, to be used not only to triage, but also to predict probability of late complications, and the development of decontamination agents that are amenable to mass casualty use. All of these emphasis areas will be discussed in more detail below and are organized in Table 1.

Depending on the stage of research, the RNCP has used a number of different funding mechanisms to support development of MCMs and biomarker discovery across a broad range of organ systems. The bulk of RNCP funding has been earmarked for early to mid-stage research. This has included grants, cooperative agreements and funding of the Centers for Medical Countermeasures Against Radiation Consortium [46], which have been continuously supported since 2005. Funding has also been provided through the establishment of Inter-Agency Agreements (IAAs) with other government research groups, such as AFRRI, the National Cancer Institute and research scientists at the FDA. In addition, support has been provided through contracts, small business awards for advanced development and through a unique offering called the Product Development Support Contract. This NIAID-supported effort, awarded to the University of Maryland School of Medicine from 2005–2015 [47–49], and to SRI International since 2015 [50], allows groups with MCM candidates or biomarkers with promising preliminary data, to discuss their product with the NIAID and potentially gain access to a range of advanced development resources. This includes studies required by the US FDA for product approval under the Animal Rule.

Regulatory aspects

Translational research for MCMs can be accelerated by addressing regulatory challenges proactively, and this approach has been a central point of US Government funding agencies. Over the past 16 years, agencies that fund radiation research have cultivated important connections with US FDA regulatory divisions responsible for review and product approval/licensure/clearance (Center for Drugs Evaluation and Research, Center for Biologics Evaluation and Research and Center for Devices for Radiological Health). These close collaborations have improved communications between the agencies, and thus, increased the speed with which approval of MCMs and biodosimetry devices for radiation injury can be achieved. The FDA's regulations concerning the approval of new drugs or biological products when human efficacy studies are neither ethical nor feasible are known as the ‘Animal Rule’ (21 CFR 314.600 for drugs; 21 CFR 601.90 for biological products). This path to FDA approval is applicable to MCMs, and it is vitally important that everyone involved in MCM development be aware of and understand these regulations [51].

The FDA and funding agencies, along with companies wishing to license MCM products, continue to work together to operate in this challenging licensure framework. US Government funding agency scientists frequently communicate with investigators about the Animal Rule, and work collaboratively to anticipate and mitigate regulatory challenges. To that end, NIAID, BARDA and FDA have co-sponsored many successful scientific conferences focused on topics such as animal model development and organ-specific [52–55] and radiation combined injuries [56], MCM advancement and repurposing [57–60], biodosimetry [61] and regulatory issues [59]. At each step of the process, RNCP program staff have interacted frequently with investigators in the funded research portfolio, to help accelerate the development process, in the hopes of advancing promising candidates toward FDA approval. This has included providing both in-house regulatory expertise from the NIAID Office of Regulatory Affairs, as well as being involved in informal and formal interactions between researchers, companies and the FDA. In many instances, approaches requiring advanced pivotal animal and human studies have been transitioned to BARDA for further development, although several have reached licensure based primarily on NIAID-funded work.

Animal models and natural history studies

In order to develop and test products for efficacy in addressing radiation-induced injuries resulting from a radiation emergency, it is necessary to develop animal models that adequately reproduce anticipated human responses (see Table 1). Studies supported by the RNCP have primarily focused on in vivo animal models, to both determine efficacy of MCMs and usefulness of different biomarkers in assessing severity of radiation-induced damage. Considerable effort and funding has gone into the establishment of both small and large models for the damage caused by radiation exposure (e.g. hematopoietic, GI, lung, skin, etc.). Several models were developed in mice and nonhuman primates (NHP) [47, 48, 62, 63] and have been used to successfully validate the ability of a number of products to improve survival following radiation exposure. Minipig [64], dog [65, 66] and rat [67] models have also been used to demonstrate product benefit for several radiation sub-syndromes. In addition, a vital resource in the quest to better understand the biological outcomes that result from radiation exposure is an RNCP-supported NHP radiation survivor colony, which is composed of rhesus macaques that have survived radiation exposure, as well as a cohort of age-matched, unirradiated controls. These irradiated NHPs, which currently number over 200 monkeys, most closely mimic expected human responses to radiation. They have been cared for at Wake Forest University since 2007, and studying them is providing valuable insights into other late effects of radiation exposure, such as immune dysfunction [68], cerebro- [69] and cardio-vascular [70] damage, cognitive deficits [71] and radiation-linked evolution of other diseases like diabetes [72, 73] and cancer. Additional animals are added to and removed from this colony every year. Through collaborations between academic, corporate and government partners, the continuum of funded research has spanned early target discovery and identification of mechanisms of radiation injury, all the way through licensure and stockpiling of therapeutics (Fig. 3).

BARDA, in addition to their focus on advanced MCM product development [1], has also taken a host-directed therapies approach, electing to develop several animal models (rabbit and minipig) to study overarching radiation injuries. Using these models, they are able to work with companies that have therapeutics with a greater systems biology impact (Fig. 4). They are investigating products that have efficacy beyond radiation injury, which include those directed toward ischemic stress, vascular injury, coagulopathies, inflammatory pathways and cell death. They have a history of providing advanced development funding of radiation MCMs, with 10 established contracts as of 2021. The BARDA strategy focuses on products that could meet the established
Table 1. Radiation Research Approaches for Mass Casualty Response Under Study in the US

### I. Animal Model Development

**Survival models**
- Small (mouse, rat)
- Large (minipig, rabbit, pig, dog, nonhuman primate)

**Radiation exposure models**
- Total-body
- Partial-body (with bone marrow sparing)
- Localized (cutaneous)

### II. Biodosimetry

**Cytogenetics**
- Dicentric assay
- Micronuclei
- Gamma-H2AX
- Automation of above methods

**Blood cell changes**
- Lymphocyte depletion kinetics
- Neutrophil/lymphocyte ratio

**'Omicstechnologies’**
- Proteomics (e.g., cytokines and other systemic or organ-specific markers)
- Genomics
- Metabolomics
- Lipidomics
- Novel approaches
- C-reactive protein
- Cytokine panels
- Telomere length

### III. Medical Countermeasures (MCMs)

**Mitigation/treatment of radiation injuries**
- H-ARS
- GI-ARS
- Lung
- Skin
- Kidney
- Vascular
- Cardiac
- Central nervous system
- Radiation combined injuries

### IV. Radionuclide Blocking/Decorporation

**Existing approaches**
- Ca-, Zn-Diethylenetriaminepentaacetic acid (DTPA)
- Prussian blue
- Improvements to licensed products
- Oral forms of DTPA
- Pediatric formulations of Prussian blue
- Novel products
- HOPO
- Lung surfactants
- Metal chelators for other radionuclides
Medical countermeasures identification and development

Although primarily tasked with early- to mid-stage research, the RNCP has been engaged in advanced product development as well, having provided funding for the Animal Rule studies and working with Amgen to gain FDA licensure of Neupogen® and Neulasta® in 2015, and Nplate® in 2021, for use in hematopoietic acute radiation syndrome (H-ARS). BARDA also supported similar licensure of Leukine® (Partner Therapeutics, originally Sanofi) in 2018. These growth factors were considered ‘low-hanging fruit,’ in that they were already licensed for oncologic indications, and are available for inclusion the Strategic National Stockpile (SNS). In addition, many approaches that had their beginnings in the RNCP portfolio have gone on to formal proceedings with the FDA, including approval of Investigational New Drug (IND) requests for MCMs, and Investigational Device Exemption (IDE) requests for biodosimetry devices. Still other products have transitioned to BARDA for follow-on support since 2006, when BARDA’s program was founded.

Neupogen®, the first drug to be approved for ARS in 2015, was already in use for several clinical indications and was stockpiled by the US Government, and had an FDA emergency IND in place. Its use for ARS, however, would have required issuance of an Emergency Use Authorization (EUA). Therefore, there was a desire to complete studies that could lead to its full approval for ARS, so that the EUA process would not be required. Impressive survival benefits were observed through NIAID and BARDA funded studies that used the three approved leukocyte growth factors, which were administered to total body-irradiated NHPs, beginning 24 to 48 hours post-irradiation [74, 75]. In addition to a survival benefit, secondary endpoints were also improved, including neutrophil counts.

Whereas G-CSF and GM-CSF target the myeloid lineages to enhance survival, another product, Nplate®, also known as romiplostim (Amgen), targets megakaryocytes to increase platelet production. Already approved by the FDA for treatment of immune thrombocytopenia, it was also shown to improve platelet counts in small [76] and large [77] animal models. Nplate®, delivered as a single dose either to mice [78] or NHPs [79], 24-hours post-irradiation, led to a significant
improvement in animal survival. In addition, as Neulasta® is an accepted standards of radiation medical management, Nplate® was also tested in combination with this growth factor, and data suggest that there could be an additive benefit [79, 80]. Nplate® was recently approved by the FDA (January 2021) to increase survival in adults and children exposed to radiation sufficient to cause H-ARS.

Although the first four drugs approved for H-ARS were drugs that were repurposed from other clinical indications [59] (primarily oncology and hematology), there is a robust pipeline of approaches that target many pathways for H-ARS, as well as other sub-syndromes, including, but not limited to, GI-ARS [81–85], skin injuries [52], late lung [53] and kidney complications [67, 86–88], cardiovascular [55], central nervous system [69, 89–91] and radiation combined injuries [92–94]. It would be challenging to list all the products that are being investigated for potential use as radiation MCMs; however, given the multi-organ dysfunction known to occur after radiation exposure, products targeting each of the affected organs (see Table 1) have been widely studied. These approaches have been reviewed elsewhere [52, 53, 56–59, 95].

**Biodosimetry markers and devices**

If a radiation mass casualty incident were to occur tomorrow, the ‘gold standards’ for assessing radiation exposure and triaging patients would be employed (see Table 1). These methods include a determination of lymphocyte depletion kinetics [96], or an evaluation of cytogenetics, such as the dicentric assay, or scoring of micronuclei [97] or the less reliable ‘time to emesis’ [98]. It is also possible that the METREPOL system for evaluation of injuries [99], mentioned above, could be put to use. Unfortunately, these techniques do have drawbacks, in terms of timing of assessment, throughput and capabilities. In terms of the next generation of research funded in the area of biodosimetry, no approaches have yet been cleared by the US FDA for use in radiation mass casualty triage. The NIAID investment in biomarker discovery and device design, as with the MCM portfolio, covers exploratory studies into novel markers, through funding of improvements of the standard cytogenetic and new ‘omics’ technologies, to contracts involving device prototypes and validation of biomarker panels (Fig. 5). Pilot projects funded through the CMCR and IAAAs provide a robust pipeline of novel biomarkers of radiation injury, whereas advanced development of biomarker panels and detection devices are supported primarily through contract awards.

Many biodosimetry products currently at BARDA received their initial funding through the RNCP, and several groups have begun interfacing with the FDA to move their products toward stockpiling. BARDA also has counterparts to their MCM portfolio in the biodosimetry space. Having worked with many contractors in this mission space, BARDA has experienced firsthand the challenges involved in advancing a device for FDA clearance. Some of these hurdles involve establishing laboratories and instrumentation for immediate response, which includes ensuring that samples and reagents can be safely moved from place to place. In addition, the testing needs to be accessible to first responders with minimal training, and the results must be robust and trustworthy. As many have learned over the course of COVID-19 testing, these challenges are not unique to biodosimetry. BARDA currently funds development of a point-of-care, field deployable test, as well as approaches, which are also needed for definitive care decisions that often take place in a hospital setting [100]. The four most advanced devices that are funded by BARDA and are nearing US FDA clearance include:

- an on-site screening test requiring only a finger stick of blood to triage those who have received little or no radiation from those who have received clinically significant levels of radiation and need further immediate patient management . . . and multiple laboratory-based, high-throughput quantitative tests, currently under development . . . to more accurately define dose levels and possibly predict cellular and organ-damage and other longer-term effects of radiation. [100]

As with the other focus areas of radiation funding, there are a number of other approaches under consideration to accurately and rapidly assess radiation dose received. For example, the US DoD, through their investment in research at AFRRI, has also made strides in identifying biomarkers of injury and developing algorithms that show promise for use during a radiation incident. These advances include the Biodosimetry Assessment Tool [101–104], which brings together a number of clinical signs and symptoms, and enables first responders and medical personnel to make estimates of a patient’s radiation dose. In addition, consideration of panels of early response markers, such as the neutrophil/lymphocyte ratio [105], serum amyloid A [106], c-reactive protein and other cytokines [107] provide a means to assess other readily-accessible biological fluids using established prognostic tools.

**Radionuclide blocking/decorporation agents**

The final of the three focus areas of the US Government to ensure radiation medical preparedness is the development of products to be used to remove, or decorporate internalized radionuclides, allowing
them to be excreted from the body [60] (see Table 1). Although there
are several licensed, stockpiled products with different mechanisms
of action (Ca- and Zn-diethylentriaminepentaacetic acid [DTPA] [both
remove plutonium, americium, uranium], Prussian blue [removes
cesium] and potassium iodide [KI] [blocks radioactive iodine uptake
by the thyroid]), their use is limited by either intravenous routes
of administration, which are not amenable to a mass casualty response, or
a limited range of radionuclides to which they bind. Based on pre-
clinical safety and efficacy studies in rodents that were funded by
the NIAID, the FDA has cleared an IND for a company that plans
to carry out human safety and pharmacokinetic studies on a novel,
oral radionuclide decontamination agent [108]. NIAID’s investment
in development of 3,4,3-Li(1,2-HOPO), a hydroxypyridinone chelating
moiety (HOPO), has led to planning for first-in-human safety studies.
HOPO appears to be superior to existing products, in that it is
given orally, has higher binding affinity, and can also remove more
radionuclides [109]. The oral formulation is also more appropriate
for use in pediatric and geriatric populations.

The US SNS represents a critical element in the storage and dis-
tribution of MCMs, in case of a radiological or nuclear public health
emergency [4]. Once drugs have been identified as being essential
for the treatment of individuals with radiation-induced injuries, they
are considered for inclusion in the stockpile. Another aspect of storage
of products is vendor-managed inventory, in which vendors are provided
compensation by the government to maintain a ‘supply bubble’ within
their own drug inventories [1]. If needed, these extra doses of product
can be quickly mobilized to where they are needed, without the need
to wait for new drug manufacture. This paradigm also means that
the government does not need to purchase and stockpile products, only
to have them expire and need to be re-purchased at a later date. Working
closely with industry has enabled the US Government to make great
strides in identifying products of value and ensuring their availability
in case of a radiation incident.

### Challenges

Perhaps the greatest challenge faced by the USA in accelerating pre-
paredness for a radiation public health emergency is incentivizing pri-
ate pharmaceutical companies to work with the government. For
many products (such as those designed to decorporate radionuclides,
or biodosimetry devices that are specific to radiation), the government
represents the primary market. Because the median cost of bringing
a new drug to the market is estimated to be $985 million [110], the US
Government seeks to leverage existing industry investments. For this
reason, the model that has been adopted in the USA involves reducing
barriers that can impede companies from engaging [3]. Functioning
as a ‘virtual pharmaceutical company,’ the major US funding agencies
have facilitated fruitful arrangements between both small and large
business concerns and the government; however, the only currently
licensed products are those that were repurposed from other clinical
indications. To date, no novel approaches have yet been approved. In
addition, the US has moved away from standard stockpiling in the SNS,
which necessitates constant replenishing of products that have reached
their expiration date. Adopting a vendor- or user-managed inventory
allows for stock to be rotated to avoid expiry [111]. However, this
approach only works when the MCM has another use, and the dosing
and formulation of the marketed product are the same.

### CONCLUSION

In closing, much has been accomplished since 2004 when the US
Government’s radiation medical response research programs were
initiated. Collegial government partnerships have allowed for more
rapid advances in drug and device development, through early and
frequent interactions and sharing of portfolio elements. Important
expertise obtained from colleges and universities, corporate and non-
government organizations have paved the way for new products.
Successful collaborations across government agencies, along with
other stakeholders have allowed for critical research gaps to be iden-
tified, which the agencies tasked with developing these approaches,
continue to address. Combined with critical lessons learned from
global partners, strategic investments of funding and guidance should
continue to yield promising products to save more lives in the wake of
a radiation incident.

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### PRESENTATION AT A CONFERENCE

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