

WORKSHOP REPORT

Challenges and Benefits of Repurposing Products for Use during a Radiation Public Health Emergency: Lessons Learned from Biological Threats and other Disease Treatments

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The risk of a radiological or nuclear public health emergency is a major growing concern of the U.S. government. To address a potential incident and ensure that the government is prepared to respond to any subsequent civilian or military casualties, the U.S. Department of Health and Human Services and the Department of Defense have been charged with the development of medical countermeasures (MCMs) to treat the acute and delayed injuries that can result from radiation exposure. Because of the limited budgets in research and development and the high costs associated with bring promising approaches from the bench through advanced product development activities, and ultimately, to regulatory approval, the U.S. government places a priority on repurposing products for which there already exists relevant safety and other important information concerning their use in humans. Generating human data can be a costly and time-consuming process; therefore, the U.S. government has interest in drugs for which such relevant information has been established (e.g., products for another indication), and in determining if they could be repurposed for use as MCMs to treat radiation injuries as well as chemical and biological insults. To explore these possibilities, the National Institute of Allergy and Infectious Diseases (NIAID) convened a workshop including U.S. government, industry and academic subject matter experts, to discuss the challenges and benefits of repurposing products for a radiation indication. Topics covered included a discussion of

U.S. government efforts (e.g. funding, stockpiling and making products available for study), as well unique regulatory and other challenges faced when repurposing patent protected or generic drugs. Other discussions involved lessons learned from industry on repurposing pre-license, pipeline products within drug development portfolios. This report reviews the information presented, as well as an overview of discussions from the meeting. © 2018 by Radiation Research Society

INTRODUCTION

The U.S. government has tasked several agencies with the mission to research, develop, license and stockpile medical countermeasures (MCMs) to treat injuries that could result from exposure to radiation during a mass casualty, public health emergency. These agencies include the Department of Health and Human Services (HHS) [National Institutes of Health (NIH), National Institute of Allergy and Infectious Diseases (NIAID), Biomedical Advanced Research and Development Authority (BARDA)], the Department of Defense (DoD) [Armed Forces Radiobiology Research Institute (AFRRI)], the Food and Drug Administration (FDA) and the Centers for Disease Control and Prevention (CDC).

Injuries suffered in the wake of a radiation public health emergency are expected to include acute radiation syndrome (ARS, encompassing primarily hematopoietic (H) and gastrointestinal (GI) complications), as well as injuries resulting at later times postirradiation, i.e., the delayed effects of acute radiation exposure (DEARE, including late GI, lung, kidney, cardiovascular and cognitive/neurological). A key complication in the development of drugs for use in case of a radiation incident is the inability to ethically

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conduct human efficacy trials. In 2002, the FDA promulgated regulations commonly referred to as *Animal Rule* [21 CFR 314.600–314.650 (drugs) or 21 CFR 601.90–601.95 (biological products)] (1) to address approval of new drugs and biological products when human efficacy studies are not ethical or feasible. The Animal Rule applies only to products² intended to prevent or reduce severity of “life-threatening conditions caused by exposure to lethal or permanently disabling toxic biological, chemical, radiological, or nuclear substances” and includes additional regulatory requirements.³ Safety in humans would still need to be demonstrated for the proposed route of administration, dosage form and formulation, and at a minimum, the proposed dose, regimen and duration of treatment proposed for use as an MCM. This pathway has been discussed in more detail elsewhere (2–5).

In addition, development of MCMs must take into consideration the expected concept of operations for use of an MCM during a mass casualty, public health emergency. Mobilizing MCMs to treatment centers within the first 24 h after an incident is anticipated to be exceedingly difficult.

Therefore, for radiation/nuclear MCMs targeted for further development for civilian use, primary efficacy end points must be clearly related to the desired benefit in humans, generally improvement in survival or prevention of major morbidity, when administered 24 h or later postirradiation. This does not exclude the need for prophylactic treatments for first responders, law enforcement and military personnel required to enter the exposure zone; however, treatment of these populations falls outside of the NIAID mission to address stockpiling needs for civilian populations.

With multiple organ systems injured by radiation, the mission space for agencies involved in MCM development is broad; necessitating that available resources are carefully conserved in identifying approaches to successfully treat patients. Because of the high costs involved in bringing a research drug into the marketplace, the U.S. government has sought to minimize some expenses by turning to products that are in clinical use for other indications. There are several reasons that the U.S. government favors a repurposing approach. These clinical products are often considered to be “low-hanging fruit”, because if the drug is used at a similar dose and dosing regimen for its new indication, it may cost less money and take less time to obtain approval/licensure, due to the potential availability of large patient safety databases. These aspects of cost and timesaving are discussed in more detail below. In addition, if a drug is in routine clinical use, physicians will have familiarity with it, and may have greater comfort prescribing

its use during a mass casualty public health emergency. Finally, due to the recurring costs involved in replenishing a government stockpile as drugs reach their expiration dates, it may be preferable to use other approaches [such as vendor or user-managed inventory (discussed below), which might be available for a licensed/approved/cleared product⁴] to ensure availability of an MCM.

Notably, there can be challenges to overcome even when repurposing products from the clinic. For example, there may be issues with the intellectual property (IP) status, and companies might be hesitant to risk discovery of adverse events associated with use of their compound for a radiation indication. These and other issues can temper enthusiasm to repurpose drugs. To explore these potential challenges, and other benefits and risks to repurposing products already in the clinic for public health emergency indications, the Radiation and Nuclear Countermeasures Program (RNCP), within the NIAID, NIH convened a workshop in Rockville, MD on August 29, 2017, bringing together representatives from the U.S. government, academic and industry researchers (Table 1). RNCP staff were joined by an interagency planning group that included individuals from the NIAID Division of Microbiology and Infectious Diseases (DMID), BARDA and the FDA. The goal of the workshop was to allow subject matter experts to consider the challenges and opportunities of repurposing products for a radiation indication. Through presentations and a guided discussion session, participants shared important regulatory experiences and highlighted ways to address potential hurdles to repurposing efforts. An overview of these talks and discussion are presented below.

BACKGROUND

The concept of repurposing is certainly not new, and recently, there has been greater emphasis placed on the benefits of this approach (6–8). The meaning of the terms repurposing and repositioning has been subject to some discussion in the literature, with the finding that most definitions involve common themes to delineate concept, action, use and product (9). Generally, and for the purposes of this meeting report, repurposing will be defined as seeking a new indication for an approach that either has already been licensed/approved/cleared for another indication, or for which extensive clinical data are already available (e.g., an approach that was under consideration for treatment of another disease but was not ultimately approved). These approaches could include drugs, biologics or devices.

There are many products that have been repurposed for other non-chemical, biological, radiological or nuclear (CBRN) injury indications (examples are listed in Table

² Throughout this text, the word “product” refers to drugs or biologics unless otherwise noted.

³ 21 CFR 314.610(b) for drugs and 21 CFR 601.91(b) for biological products.

⁴ As per FDA nomenclature, biological products are licensed, drugs are approved, and devices are cleared. As used in this report, the term approval refers to approval or licensure.

TABLE 1
Workshop Speakers and Areas of Expertise^a

| Name | Affiliation | Areas of expertise |
|---------------------------------|---|--|
| David Cassatt, PhD | RNCP, NIAID, NIH, Rockville, MD | Toxicology, product development, MCMs, immunology |
| Janet Chow, PhD | Regulatory Affairs, Amgen, Thousand Oaks, CA | Regulatory affairs, biotechnology, neuroscience |
| Eric Cohen, MD | University of Maryland School of Medicine, Baltimore, MD | Radiation-induced renal injury, ACE inhibitors, clinical trials |
| Christine Colvis, PhD | NCATS, NIH, Bethesda, MD | Drug development partnership programs |
| Andrea DiCarlo, PhD | RNCP, DAIT, NIAID, NIH, Rockville, MD | Radiobiology, product development, MCM testing |
| John Dykstra | Humanetics Corporation, Edina, MD | Drug development, CMC, regulatory affairs |
| John Griffin, MD | Scripps Research Institute, La Jolla, CA | Cytoprotective protein C pathway, blood proteins, lipids, thrombosis |
| Mary Homer, PhD | BARDA, HHS, Washington, DC | Radiation MCM development |
| Juliann Kiang, PhD | AFRRI, DoD, Bethesda, MD | Animal models and MCMs testing for radiation alone and radiation combined injuries |
| Sanjay Kumar, PhD | R & D Alternative Discovery & Development, GlaxoSmithKline, King of Prussia, PA | Drug discovery and early development activities for both small and large molecules |
| Meetha Medhora, PhD | Medical College of Wisconsin, Milwaukee, WI | Mitigation of radiation lung injuries, ACE inhibitors |
| Andrea Powell, PhD ^b | CTECS, CDER, FDA, White Oak, MD | FDA's Animal Rule, MCM development |
| Paul Price, PhD | ORA, NIAID, NIH, Rockville, MD | Regulatory affairs, immunology, drug discovery and development |
| Robert Segal, MD | Windtree Therapeutics Inc., Warrington Township, PA | Surfactants, neonatal lung, product development |
| Oxana Selivanova, PhD | BARDA, HHS, Washington, DC | Regulatory affairs, CMC, drug development, pharmaceutical sciences |
| Mark Williams, PhD | OBRTR, DMID, NIAID, NIH, Rockville, MD | Animal models of infectious diseases, MCM testing |
| Yon Yu, PharmD | Regulatory Affairs, CDC, Atlanta, GA | Regulatory affairs, preparedness, emerging infections, SNS |

^a Speakers (except as noted) reviewed this meeting report prior to journal submission.

^b Workshop participant was not able to review the report prior to journal submission.

2). Some successful repurposing efforts have been the result of happenstance (e.g., chance findings noted in clinical trials for another indication), while others have come about due to targeting common mechanisms of action between an original and new indication. In addition, some drugs are repurposed as part of the normal course of drug development, where a drug may fail to meet its initial indication but is effective for a different indication. One notable example is the licensure of Viagra[®] for erectile dysfunction, which was originally developed (although not approved) as a

TABLE 2
Examples of Successfully Repurposed Products for Non-CBRN Indications

| Brand name | Product name(s) | Original manufacturer | Mechanism of action | Original indication | Repurposed indication | Ref.(s) |
|-------------------------|---------------------------------|-----------------------|--------------------------------|--|---------------------------|------------|
| Retrovir | Zidovudine/azidothymidine (AZT) | GlaxoSmithKline | Retrovirus inhibitor | Anti-cancer drug (not further pursued) | HIV infection | (107) |
| Viagra | Sildenafil citrate | Pfizer | Phosphodiesterase inhibitor | Angina (not further pursued) | Erectile dysfunction | (7) |
| Celebrex [®] | Celecoxib | Pfizer | Nonsteroidal anti-inflammatory | Osteoarthritis | Colorectal polyps | (108) |
| Rapamune [®] | Sirolimus | Pfizer | mTOR inhibitor | Advanced renal cancer carcinoma | Breast cancer | (109) |
| Avastin [®] | Bevacizumab | Genentech Inc. | Anti-angiogenic | Metastatic breast cancer | Wet macular degeneration | (110) |
| Glucophage [®] | Metformin | Bristol-Myers Squibb | Anti-hyperglycemic agent | Type 2 diabetes | Cancer | (111) |
| Rogaine [®] | Minoxidil | Johnson & Johnson | Potassium channel opener | High blood pressure | Hair loss | (112) |
| Requip [®] | Ropinirole | GlaxoSmithKline | Non-ergoline dopamine agonist | Parkinson's disease | Restless leg syndrome | (113) |
| Thalomid [®] | Thalidomide | Celgene | Anti-angiogenic | Anti-nausea | Leprosy; multiple myeloma | (114, 115) |

treatment for chest pain. Further, the drug is now being considered to treat malaria as well. A similar example is Retrovir® (zidovudine or azidothymidine, AZT), which failed to inhibit growth of cancer cells, for which it had been specifically designed; however, it effectively inhibited the HIV virus and was repurposed as a treatment for AIDS. Several excellent review articles are available, which document repurposing efforts that have been successfully undertaken (10–12).

There have already been successes in repurposing efforts throughout the CBRN MCM portfolio. These products include Neupogen® [filgrastim; granulocyte colony-stimulating factor (G-CSF)] and Neulasta® [pegfilgrastim; pegylated (PEG) G-CSF] in 2015 (both from Amgen® Inc., Thousand Oaks, CA) and Leukine® [sargramostim; granulocyte-macrophage colony-stimulating factor (GM-CSF)] in 2018 [Partner Therapeutics (previously Sanofi), Boston, MA], all of which were initially approved for neutropenia in oncology patients and are now approved products to treat H-ARS. For other CBRN indications, antibiotics for inhalational anthrax (i.e., doxycycline, ciprofloxacin, levofloxacin and penicillin G) (13) and pyridostigmine bromide for nerve gas exposure have also been approved (<https://bit.ly/2vXrgp4>). Since Neupogen and Neulasta were already approved for other indications, these drugs became early candidates for the repurposing effort driven by the U.S. government. G-CSF stimulates hematopoietic cell precursors to differentiate into neutrophils and mobilize to injury sites, decreasing the incidence of infection. In 2004, the Strategic National Stockpile (SNS) Radiation Working Group recommended that cytokine therapies such as G-CSF, and GM-CSF be provided to people exposed to radiation during a mass casualty incident (14). However, unless these products obtained FDA licensure for H-ARS, their use in a mass casualty scenario would be limited. Taken together, these early repurposing achievements have led to an increased emphasis on identifying other products that could be used in the CBRN arena.

The NIAID spent an estimated \$10 to \$20 million each to undertake animal rule experiments that were necessary to bring the already approved Neupogen and Neulasta growth factors to the FDA for consideration as MCMs for H-ARS (D. Cassatt). There were also costs incurred by Amgen to extend the label indication for both drugs. Nonetheless, these costs are far less than the estimated \$648 million (<https://bit.ly/2vw19Hp>) to \$2.5 billion (<https://bit.ly/2rmjkK4>) needed to gain licensure/approval for a new approach obtained through standard FDA regulatory pathways. Since no new chemical entity has yet been approved by the FDA using the Animal Rule pathway (<https://bit.ly/2MqlMNN>) (only repurposed products to date), it is unknown precisely what costs would be involved. In terms of the timeline advantages of repurposing, this licensing of the first two MCMs for H-ARS took more than ten years, even though they were already in

heavy clinical use for a related indication. When these efforts were initiated in 2004, there were only a few animal models in early development that needed further investment. The same holds true for the availability of facilities and expertise to perform the necessary experiments. Finally, the reality is that there is limited U.S. government radiation MCM funding available, and it is difficult to incentivize companies to enter the MCM development space. However, given recent MCM approvals for radiation threats, there has been increasing willingness on the part of companies to engage with the U.S. government in these efforts, so there is hope that this process will be accelerated moving forward.

MEETING PROGRAM OVERVIEW⁵

This one-day workshop brought together participants to address the challenges and benefits of repurposing products for a radiation indication. Knowledge gained from prior approvals of radiation-specific drugs was supplemented with examples of approvals from other CBRN mission spaces, as well as examples of industry approaches to develop products from within their research pipeline that were abandoned for other indications. In addition, a U.S. government program aimed at making industry drugs available outside of the company that initially developed them was discussed. The structure of the meeting was such that U.S. government perspectives were discussed in Session I, followed by a consideration of repurposing of drugs still under patent protection (Session II, see Table 3) and new indications for generic (off-patent) compounds (Session III, See Table 3). A guided participant discussion followed Session III. An overview of the content presented in each session is provided below.

Session I: Roles of U.S. Government Agencies Involved in Repurposing

As discussed in the introduction, many agencies within the U.S. government work together closely, with the shared mission to accelerate the research, product development and licensure of candidate products for CBRN indications. The NIH, DoD and BARDA are responsible for providing research and development funding and expertise, with the NIAID focused on approaches in an earlier stage of research and supporting early clinical studies, and BARDA focused primarily on later stage development as well as procurement of MCMs for the SNS. The mission of the DoD includes early and late-stage development, with a focus on military and support personnel, as well as sharing important information with the NIH and BARDA. Once sufficient research data have been obtained, the FDA is responsible for assuring the MCM meets the legal and regulatory

⁵ Where pre-publication data are discussed, the investigator's first initial and last name, to whom the information is attributed, is provided in parentheses.

TABLE 3
Repurposed Drugs, Biologics and Devices under Study for Possible Use in a Radiation Public Health Emergency
(as Presented during the Meeting)^a

| Drug/biologic/device name | Current manufacturer | Mechanism of action | Original indication | Date of approval, licensure or clearance | Status for repurposed indication |
|--|-----------------------|--|--|--|---|
| Neupogen (G-CSF; filgrastim) | Amgen | Growth factor | Chemotherapy-induced neutropenia | 1991 | Licensed (sBLA) for H-ARS in 2015 |
| Neulasta (PEG-G-CSF; pegfilgrastim) | Amgen | Growth factor | Chemotherapy-induced neutropenia | 2002 | Licensed (sBLA) for H-ARS in 2015 |
| Leukine (GM-CSF; sargramostim) | Partner Therapeutics | Growth factor | Chemotherapy-induced neutropenia | 1991 | Licensed (sBLA) for H-ARS in 2015 |
| Xigris (Drotrecogin alfa; activated protein C) | Eli Lilly | Anticoagulant, anti-inflammatory, pro-fibrinolytic | Sepsis | 2002; withdrawn 2011 | BARDA-funded for H-ARS |
| Silverlon (calcium alginate dressing) | Argentum Medical LLC | Silver inhibition of infection | Wound and burn contact dressing | 1998 | BARDA-funded for cutaneous radiation injuries |
| Mozobil (plerixafor) | Sanofi | Anti-angiogenic | Non-Hodgkin's lymphoma, multiple myeloma | 2008 | NIAID-funded for H-ARS |
| Surfaxin (lucinactant) | Windtree Therapeutics | Lung surfactant | Neonatal respiratory distress | 2012 | NIAID-funded for radiation lung injury |
| Vasotec [®] (enalapril) | Merck | ACE ^b inhibitor | Hypertension | 1981 | NIAID-funded for kidney and lung radiation injuries |
| Capoten [®] (captopril) | Squibb (BMS) | ACE ^b inhibitor | Hypertension | 1981 | NIAID-funded for kidney and lung radiation injuries |
| Prinivil [®] (lisinopril) | Merck | ACE ^b inhibitor | Hypertension | 1987 | NIAID-funded for kidney and lung radiation injuries |
| Ciprofloxacin (fluoroquinolone) | Bayer | Antibiotic | Infection | 1987 | NIAID-funded for radiation combined injury |

^a Other drugs have been studied using U.S. government funding; however, because presentations were not made during the meeting, they are not included here.

^b Angiotensin-converting enzyme.

requirements for safety and efficacy, and for approving the MCM for use, often via the FDA Animal Rule. The CDC, with past responsibility to provide for the storage and distribution of any MCM [although this role is now changing (<https://bit.ly/2vxU08m>)], is an important collaborator with all the other agencies outlined above, in the Public Health Emergency Medical Countermeasures Enterprise (PHEMCE). The interactions of these groups are what enable the U.S. government to enhance MCM preparedness for CBRN threats and emerging infectious diseases.

Food and Drug Administration. In approaching the FDA to seek approval/licensure/clearance to repurpose a product already in clinical use for another indication, or for which clinical data are available, but the product is not yet approved, it is important to understand what entity holds the IP for use of the drug, and if there is an interest in obtaining a new indication. The proposed pathway for licensure can depend on whether the approach to be repurposed is still under patent and/or exclusivity protection. This status can be determined by accessing the FDA website (<https://bit.ly/2KCEHQs>) as well as the FDA/Center for Drugs Evaluation and Research (CDER) Small Business and Industry Assistance (SBIA) Chronicles, Patents and Exclusivity

Issue (15). If only generic versions are available, it is important to determine if a generic company is interested in providing support for the new indication.

This effort might include a determination as to whether the innovator will provide a right of reference to their data, if needed; if any information gaps need to be addressed to support the new indication; and how data will be generated for the new indication, to bridge to the approved product. As an available resource, the FDA maintains two sets of listings of approved products. These include the Orange Book: Approved Drug Products with Therapeutic equivalence evaluations (16) and the Purple Book: Lists of Licensed Biological Products (17), which discusses product exclusivity and biosimilarity evaluations. A request for orphan drug designation (ODD), designed for drugs and biologics used to treat rare diseases or conditions (defined as one that affects fewer than 200,000 people per year in the U.S., or more than 200,000 if there is no expectation of recovery of development costs) might also be considered (e-CFR 21 PART 316 Orphan Drug & the Orphan Drug Act 1983). Some important incentives of ODD include seven years of marketing exclusivity, tax credits and waiver of user fees (18).

Adding to the ability to have MCMs considered for approval via the Animal Rule is the FDA's addition of animal models to the Drug Development Tools (DDT) Qualification Program (<https://bit.ly/2nsu16V>). This aspect of the program, detailed in the Animal Rule guidance, makes available FDA-qualified models for use in efficacy testing in development programs for multiple investigational drugs for the same targeted disease or condition (1). Having these models available will further accelerate the licensure process for repurposing drugs in clinical use.

National Institute of Allergy and Infectious Diseases, National Institutes of Health. There are several divisions within the NIAID with responsibility for advancing research and development of MCMs for CBRN injuries, including the Division of Allergy, Immunology and Transplantation (DAIT) and the Division of Microbiology and Infectious Diseases (DMID). The RNCP, within DAIT, oversees a funded portfolio of MCMs to treat biological damage caused by radiation exposure (19, 20). The RNCP funds the development of many novel MCMs, as well studies on licensed products to treat both ARS and DEARE (A. DiCarlo). These drugs fall into several major classes, associated with their known mechanisms of action. These categories include, but are not limited to antibiotics (21, 22), anti-inflammatories [e.g., celecoxib (23) and steroids (<https://bit.ly/2vyt08B>)],⁶ growth factors and mimetics (24–27), hormones [e.g., somatostatin (28) and parathyroid hormone (<https://bit.ly/2AWSi5A>)], interleukins (29–31), statins (32) and angiotensin-converting-enzyme (ACE) inhibitors (33, 34).

From program inception through 2017, the NIAID portfolio has included funding to explore radiation indications for more than 40 FDA-approved drugs, and studies on other products in clinical use continue to be added. The RNCP has also engaged in outreach efforts, to explore other approved drugs that might have efficacy for radiation-induced injuries. Other drugs with mechanisms of action that are also desirable to mitigate radiation injuries include those for idiopathic pulmonary fibrosis (IPF) and idiopathic thrombocytopenic purpura (ITP), gastrointestinal ulcers, anemia, as well as drugs such as steroids, kinase inhibitors and N-methyl-D-aspartate (NMDA) receptor antagonists. For example, studies (not supported by the NIAID) that were done in 2008 and 2010 using a mouse model of radiation-induced injury after whole-thorax lung irradiation (WTLI) demonstrated that postirradiation administration of Gleevec® (imatinib mesylate; Novartis, Basel, Switzerland), an oral, tyrosine kinase inhibitor initially approved for treatment of chronic myelogenous leukemia, led to a statistically-significant ($P < 0.01$) increase in survival in rodents (35, 36). As the NIAID's MCM portfolio grows, the

RNCP will continue to place emphasis on advancing drugs that have another clinical indication (either approved or in process).

In addition to MCMs under development within DAIT, many approaches for treatment of biological pathogens of concern are funded through the DMID, specifically the Office of Biodefense Research Resources and Translational Research (OBRTR) (M. Williams). The office is responsible for the provision of animal models and reagents for research, as well as services that allow for screening and development of a wide range of MCMs infectious diseases. The DMID, in collaboration with the FDA, has repurposed approved antibiotics by testing them for efficacy under the Animal Rule.

These antibiotics had extensive clinical data in humans, including pharmacokinetics (PK), safety and toxicity and dosage information, so approval required efficacy data from animals, since clinical trials are not feasible. The NIAID has extensive experience in developing and refining animal models for anthrax, plague and tularemia, and have utilized them for repurposing approved antibiotics. More recent efforts have screened potential therapeutics for Ebola, where characterization of the assays and models is ongoing (37, 38).

The DMID is pursuing qualification for animal models of anthrax, plague and tularemia, and the RNCP is working to qualify a rhesus macaque model of H-ARS (A. DiCarlo).⁷ The animal model for pneumonic plague utilizes aerosol exposure of the African green monkey (*Chlorocebus aethiops*) to 100 LD₅₀ *Yersinia pestis* strain CO92, with treatment at onset of fever, as detected by telemetry (39). This model has been used to support new indications for three antibiotics: levofloxacin (2012), ciprofloxacin (2015) and moxifloxacin (2015) (40). The tularemia animal model being proposed for qualification presents an interesting case. The cynomolgus macaque (*Macaca fascicularis*), challenged via aerosol with a target dose of 100 LD₅₀ using *Francisella tularensis* Schu S4, has been extensively characterized and found to be comparable to human disease (41). Unlike most of the highly lethal agents, there are controlled human data for tularemia. During the 1960s, U.S. Army volunteers were exposed to aerosolized *Francisella tularensis* under controlled clinical testing as part of a biomedical research program called Operation Whitecoat (42). Analysis of the data from these human studies reinforces that disease end points established in the cynomolgus macaque model of pneumonic tularemia replicate much of the disease pathology in humans. All of these experiences of the NIAID in advancing of indications for products to treat infectious diseases provide a roadmap for the repurposing of other products as radiation MCMs.

⁶ Georges G, et al. Post-exposure oral 17,21-beclomethasone dipropionate (BDP) improves survival in a canine gastrointestinal acute radiation syndrome (GI-ARS) model. 58th Annual Meeting of the Radiation Research Society; San Juan, Puerto Rico: 2012.

⁷ For the H-ARS model, staff turnover, shifting priorities and lack of continued funding have led to delays in qualification; however, communications with the FDA have continued and other areas of effort are ongoing.

National Center for Advancing Translational Sciences, NIH. The National Center for Advancing Translational Sciences (NCATS) has in place a repurposing program (C. Colvis), which focuses on investigational drugs and biologics that have been through preclinical development and Phase 1 (<https://ncats.nih.gov/ntu>).

This program represents a novel mechanism to bring drugs with clinical data into the CBRN mission space. Furthermore, it aims to demonstrate the utility of partnerships among industry, government and academia in accelerating the development of new uses for investigational products (assets). This is accomplished by industry identification of assets that they are not pursuing, and signing a memorandum of understanding with NCATS governing the testing of these assets. The assets are publicized on the NCATS website (<https://bit.ly/2vrK5RJ>) along with their mechanism of action, so that academic investigators can propose ideas for new therapeutic uses. Awards are made through a two-step process comprised of a short application that, if accepted, moves to a collaborative application with the drug/biologic sponsor, where NCATS will fund a phase II trial. One example of a success of this program is a project where a *fyn* kinase inhibitor, originally developed for cancer, is being developed for Alzheimer's disease. Using this mechanism of support, data from the work of Strittmatter and colleagues have been published on a potential role of *fyn* kinase signaling in a transgenic mouse model of Alzheimer's disease (43). AZD0530, a *fyn* kinase inhibitor developed by AstraZeneca (Cambridge, UK), was studied in mice, and was found to reverse memory deficits and rescue synaptic density loss after four weeks of treatment (44). A phase II study is in progress (<https://bit.ly/2AW4C5V>). This exemplifies the potential of this program, where a new target for Alzheimer's disease could be rapidly tested with an existing asset, hopefully leading to faster translation to therapy.

Biomedical Advanced Research and Development Authority. BARDA has supported the FDA approval/clearance for many MCM products across a variety of CBRN threats, with roles spanning MCM development, procurement and inventory management (M. Homer). For late-stage development of MCMs, BARDA continues to support and develop appropriate large animal models for ARS to assess efficacy as well as biomarkers of radiation injury and recovery, including a recent focus on the minipig. While no single animal model completely represents the human response to radiation, each model provides some relevance and limitations, especially in regards to secondary end points and biomarkers that support the primary end point of reduction in all-cause mortality. Inclusive of activities through 2017, BARDA was involved with the approval/licensure of 31 MCMs, with 15 products stockpiled for use in the event of a public health emergency.

In addition, funding from BARDA is providing for accumulation of additional data to support the repurposing

of other products and devices, including a Silverlon® product (Argentum Medical LLC, Geneva, IL), currently under development for cutaneous radiation injuries (discussed below). The BARDA model utilizes novel public-private partnerships and works to address market failures to bridge the pharmaceutical development's valley of death and bring necessary MCMs to production and market.

Early BARDA programs focused primarily on establishing a stockpile of MCMs for preparedness. For MCMs with no other utility in the commercial market, "buy and hold" is the only option for maintaining preparedness by the U.S. government. The limited strategy involves the SNS taking control of a product, with plans for immediate deployment upon request after a public health emergency. When the product reaches its expiry, it is then discarded and involves a costly re-procurement to maintain preparedness. For products already approved for commercial indications, vendor-managed inventory (VMI) can be an option; the product is stored in a vendor's warehouse and, to avoid expiry, the specific stock is rotated back into the commercial market when new stock is manufactured. Another alternative is user-managed, where the product is stored at end-user sites such as hospitals, pharmacies and emergency transport vehicles where stock is used quickly to avoid expiry. Under a VMI or user-managed inventory or contract, the vendor ensures that the specified quantity allocated for the U.S. government is maintained under appropriate storage conditions, never expires and is available for U.S. government pickup within hours after a public health emergency. Of course, these approaches only work when a product is already approved, or in late-stage development, such that it can be repurposed as an MCM and reduce the overall life cycle costs of development, procurement and sustainment.

BARDA has used this strategy in collaboration with the CDC for managing the stockpile of G-CSF/GM-CSF growth factors to treat neutropenia after an improvised nuclear device incident. The contract with the vendors includes an initial product quantity purchase, with options to make additional purchases, with VMI management over a five-year life. Products held under a VMI contract are included in the SNS inventory system and are maintained in a status for quick deployment. Within hours of an incident, the U.S. government can transport the product to the incident site.

Centers for Disease Control and Prevention. At the time of the meeting, the primary role of the CDC, in addition to performing critical research, was to facilitate availability of drugs developed as CBRN MCMs and procured for stockpiling via the CDC's SNS (Y. Yu). This role includes responsibilities that are clinical, regulatory (in conjunction with the FDA) and logistical. Currently, assets within the SNS include FDA-approved MCMs for both approved and off-label indications, as well as investigational (unapproved) MCMs.

Stockpiling of approved, licensed or FDA-approved/cleared products, used under an investigational new drug (IND) or under an Emergency Use Authorization (EUA), is protected by Public Readiness and Emergency Protection (PREP) act of 2005, which provides immunity from liability for claims of loss caused by MCMs against “threats of public health emergencies” (<https://bit.ly/2Mdnxxx>). The CDC also reviews existing data for MCM use, to prepare, submit and update INDs and EUAs for the FDA. Whereas INDs provide an exemption from the legal requirement for products to be FDA-approved prior to interstate shipment and administration in humans, and thereby allows for clinical access and repurposing of stockpile products, EUAs allow for use of approved products for unapproved uses. There are also examples of expanded-access INDs which are used for investigational MCMs that have been stockpiled during their developmental pathway. Examples of expanded access have included Neupogen (G-CSF), ciprofloxacin, Anthrasil™ (anthrax immune globulin), and heptavalent botulism antitoxin (Y. Yu).

The EUA is authority given to the commissioner of the FDA to allow for emergency use of unapproved MCMs or an unapproved use of an approved MCM. Although the FDA issues the EUA, the CDC carries out the mobilization of the drug. The FDA has provided formal guidance for industry and other stakeholders on EUA and related authorities (45), and continuously-updated information, including current actions, is also available online at the FDA’s MCM Emergency Use Authorities Website (<https://bit.ly/2M9qnoc>). EUA authorities include, among other things, shelf-life extension and emergency use instructions (EUIs). Shelf-life extension allows the FDA to extend the labeled expiration date, and EUIs permit a designated HHS official to create and issue emergency instructions with details for treating physicians concerning the FDA-approved use for a CBRN indication. The EUIs might outline to whom the product can be given, as well as information concerning how to administer the product. An EUI can only be issued for products in routine use for other indications, which is why repurposing is so important. For example, drugs that could be eligible for an EUI include use of Neupogen with modified dosing (e.g., pediatric), Tamiflu® (oseltamivir) for influenza, Radiogardase® (Prussian blue) use in infants and toddlers, or the anthrax vaccine in a dose-sparing regimen.

Session II: FDA-Approved, Patent-Protected Products and Pharmaceutical Company Approaches

Because of the different situation faced by developers looking to repurpose a product to counter CBRN threats, when the approach in question is still under patent protection (i.e., a brand name product), the challenges and benefits of repurposing these types of drugs (as opposed to generic products) is considered separately, including background and insight into the processes used by larger

pharmaceutical companies to repurpose products within their internal development pipelines.

Neupogen and Neulasta. As mentioned above, the first products approved specifically for H-ARS were Neupogen (filgrastim) and Neulasta (pegfilgrastim), two G-CSF products, both of which extended their label indications in 2015 (D. Cassatt, J. Chow, P.W. Price). Beginning in 2004, meetings were held between Amgen, the NIAID, CDER and FDA to discuss the pathway for approval under a supplemental biologics licensing agreement (sBLA) for a radiation indication. Since sufficient human safety data had been obtained during the products’ long commercial history, the FDA agreed to licensing via the Animal Rule. From these discussions, filgrastim studies in mice and an adequate and well-controlled non-human primate (NHP) efficacy study were designed and performed under an NIAID contract to the University of Maryland School of Medicine (46). Starting 24 h after LD_{50/60} irradiation, rhesus macaques were given either G-CSF or placebo daily, until neutrophil recovery. Animals also received medical management to simulate patient care (47). The selected primary end point was all-cause mortality, with secondary end points such as neutrophil recovery to support mechanism of action. Animals showed improvement in survival from 41% in the control arm to 79% in the treatment arm and significant acceleration of neutrophil recovery. The final report, as well as a report for the natural history of radiation injury in NHPs, was submitted to the FDA in 2011, along with several mouse study reports supporting filgrastim efficacy in H-ARS.

In 2013, the FDA convened an Advisory Committee meeting (<https://bit.ly/2Mx4WcC>) to discuss use of currently approved leukocyte growth factors for treatment of radiation-induced myelosuppression after a radiation incident. By a 17–1 vote, the committee agreed that filgrastim was reasonably likely to produce clinical benefits in humans exposed to radiation that is likely to induce myelosuppression during or after a radiologic or nuclear incident. Amgen obtained a letter of cross reference to access the NIAID reports and submitted a sBLA to the FDA, which resulted in approval by the FDA in March 2015, of Neupogen for use in both pediatric and adult patients with H-ARS. One challenge faced by the FDA and Amgen was to determine an effective dose to be used in humans.

Modeling PK data in humans and NHPs, in conjunction with efficacy data from the monkey efficacy study, indicated that a dose of 10 µg/kg of filgrastim would be appropriate (48). After the G-CSF study in NHP, efficacy of pegfilgrastim, dosed 1 and 8 days after irradiation, was tested in this same NHP model of H-ARS (49), and was shown to improve survival from 48% in the control arm to 91% in the treatment arm, with a similar improvement in neutrophil recovery. Using these data, along with PK and pharmacodynamics (PD) information and clinical experience, Amgen received approval of Neulasta for patients with H-ARS in November 2015. It should be noted that

since the date of this meeting, Sanofi has also received approval of Leukine for patients with H-ARS (March 2018).

These examples show the advantages of repurposing widely used products that have a large amount of clinical data and the experience associated with their use in millions of patients. The mechanism of injury due to neutropenia and the mechanism of action of G-CSF are reasonably well understood, and NHP studies demonstrated that G-CSF administration enhances neutrophil recovery and increases survival. The NHP model used to demonstrate efficacy, as well as the mouse model used to support the NHP data, are reasonably well understood. Furthermore, PK, safety and efficacy data allowed for modeling to obtain an effective dose in humans.

Xigris[®]. A therapeutic biologic that had previously received FDA approval for treatment of severe sepsis, activated protein C (APC) is another product that is now being studied as a radiation mitigator. Although initially approved in 2001, a later clinical trial showed that the product performed no better than placebo, which led to its withdrawal in 2011 (50). APC is an endogenous enzyme involved in various cell-signaling pathways. It continues to be under investigation for several human tissue injury conditions, including inflammation in lung, kidney and gastrointestinal tract, ischemia/reperfusion in kidney, heart and brain, sepsis, hemorrhagic fever and diabetes, as well as radiation injury (J. Griffin) (51). The ameliorative effects could be due to a combination of three mechanisms: activation of clotting factors, protection of the endothelium and regenerative properties (52). The Scripps Research Institute (La Jolla, CA) has been studying use of this biologic as a radiation MCM.

In a preliminary experiment, recombinant mouse APC was administered intravenously, once (at 30 min) or three times (30 min, 1 h and 2 h) after irradiation of C57BL/6 mice at 9 and 10 Gy, respectively. Administration of APC in both treatment regimens resulted in enhanced survival over vehicle. To more nearly match a possible mass-casualty scenario, a follow-up study was done, in which mice were irradiated with 9.5 Gy and given vehicle or APC (0.4 mg/kg) at 24 and 48 h postirradiation. In this study, APC administration significantly enhanced survival. In these mice, significantly higher levels of hematopoietic progenitor cells in the bone marrows of treated mice, as measured by flow cytometry or colony-forming unit assays, were also observed (53). Although species specificity could be a challenge, these data show that APC could be a promising MCM for H-ARS.

Silverlon. Radiological and nuclear incidents are expected to result in trauma, thermal burns, ARS and cutaneous radiation injuries. Cutaneous radiation exposure may exert damage to the basal cell layer of the skin and result in inflammation, erythema and dry or moist desquamation. The prevention of wound burn infection is critical, especially during the first 72 h after detonation. Silverlon wound and burn contact dressings are silver-nylon dressings

that have replaced Silvadene cream in burn blast kits currently stockpiled to treat first- and second-degree burns.

Silverlon dressings are user friendly, available in multiple sizes and have five-year shelf-life stability at room temperature. When activated by moisture, the embedded silver ions in Silverlon dressing act as an antimicrobial barrier, preventing infection to skin burn injury. Silverlon has been used for burns in military casualties, and a 10-year retrospective analysis has shown that the dressing can reduce nonirradiated wound infection rates (irradiated wounds were not studied) (54). BARDA is repurposing the existing Silverlon product line of burn and wound dressings for use in mass-casualty incidents resulting from chemical, thermal and radiological exposure (O. Selivano-va). This repurposing strategy will expand the labeling indication for the Silverlon product line to accommodate a wider therapeutic range for burn and skin injuries. Silverlon repurposing allows 510 (k) FDA pathway for both cutaneous sulfur mustard and radiation injuries. Silverlon wound dressings have been cleared by FDA and have been on the commercial market since 1998.

Mozobil[®]. A representative from Humanetics Corporation (Edina, MN) spoke about the company's repurposing program for Mozobil, a drug that was FDA-approved in 2008 (J. Dykstra). As stated on its label, Mozobil (also known as plerixafor), a hematopoietic stem cell mobilizer, is indicated in combination with G-CSF to mobilize hematopoietic stem cells to the peripheral blood for collection and subsequent autologous transplantation in patients with non-Hodgkin's lymphoma and multiple myeloma (<https://bit.ly/2nokBAb>). The drug elevates circulating hematopoietic progenitor cells by facilitating release from the bone marrow. It is approved to increase harvestable CD34⁺ cells during apheresis for autologous stem cell transplants, which is important because a portion of the population are poor mobilizers (55). Efficacy was demonstrated in published data of Mozobil phase III trial, in which Mozobil plus G-CSF significantly increased circulating CD34⁺ cells in patients over G-CSF alone. In addition, the time to achieve cell count targets of 5×10^6 CD34⁺ cells/kg was significantly reduced in the cohort receiving Mozobil (56).

Humanetics' hypothesis is that Mozobil combined with G-CSF will increase the absolute number and rate of increase of CD34⁺ cells in peripheral blood, resulting in more rapid recovery of neutrophils and other blood cell types and thus leading to better outcomes in individuals exposed to myelosuppressive doses of radiation; adding to this is that Mozobil should improve efficacy for poor mobilizers in the population and should allow dose sparing of G-CSF (J. Dykstra). In addition, published animal studies indicate that G-CSF therapy requires initiation of treatment at 24 h to be effective after exposure to 7.5 Gy as well as intensive medical management (47, 49, 57, 58). It is possible that addition of Mozobil may allow more time to initiate treatment postirradiation, thereby maintaining efficacy with less supportive care (J. Dykstra). The regulatory

twist in this narrative is that Humanetics is not the innovator/new drug application (NDA) holder for Mozobil, nor do they currently have an agreement in place with the NDA holder, Sanofi. In this situation, a company needs to rely on data from studies that they did not conduct, and for which they may not have right of reference (59), perhaps having only access to publicly-available labeling of the existing drug and study data. This situation involves some unique regulatory needs, including studies to fill data gaps for the new indication, a new product supply with a scientific bridge to the approved product (generally a bioavailability or bioequivalence study) and a patent certification/statement of non-infringement.

Surfaxin[®]/*Aerosurf*[®]. Windtree Therapeutics (formerly Discovery Labs, Warrington, PA), a biotech company focused on pulmonary critical care, is pursuing repurposing of their KL4, neonatal lung surfactant as a mitigator for radiation-induced lung injury (R. Segal). Their product portfolio includes two products: Surfaxin (lucinactant; KL4 surfactant), an FDA-approved (in 2012) synthetic peptide-containing surfactant for respiratory distress syndrome (RDS) in preterm infants; and Aerosurf (lucinactant for inhalation), a product-device combination therapy that administers the aerosolized KL4 surfactant using a proprietary method.

This device allows for high, consistent and controllable KL4 surfactant output rates with generation of small aerosol particles. Neonatal RDS occurs in infants whose lungs have not yet fully developed. The disease is mainly caused by a lack of surfactant, which helps the lungs fill with air and keeps the air sacs from deflating. Surfactant is present when the lungs are fully developed. Beginning in 2012, Windtree received Small Business Innovation Research (SBIR) phase I funding from the NIAID to study the product for treatment of radiation-induced lung injury. In a targeted mouse model involving whole-thorax irradiation, animals received 13.5 Gy single-fraction X rays, with aerosolized KL4 delivered 24 h later and daily for two weeks by intranasal administration. These studies demonstrated preservation of lung function (e.g. reduced lung inflammation and oxidative stress) (60), as well as significant improvement in survival in KL4-treated mice at 180 days postirradiation (the time frame for assessing radiation-induced lung fibrosis) (survival data are unpublished; R. Segal). Initial SBIR funding led to phase II and phase IIB SBIR awards, as well as follow-up support from other areas of the RNCP portfolio, and the NIH Chemical Defense Program (Countermeasures Against Chemical Threats (CounterACT)).

The product is also currently undergoing testing for treatment of H1N1 and H5N1 influenza infections. The fact that the product under study has already been approved for a neonatal population is testament to its safety profile, and could allow for the approval of the product for a radiation indication in pediatric as well as adult populations.

Repurposing Investigational Assets for Other Indications: GlaxoSmithKline (King of Prussia, PA). Meeting

organizers reached out to industry to learn more about how pharmaceutical companies routinely assess their internal product pipelines to identify potential compounds for repurposing. Interest in identifying new indications for existing candidate products in pharmaceutical companies stems from a general belief that for any given product, there exists an appropriate target, but the challenge is to find the right indication (S. Kumar). Thus, repurposing candidate compounds is a growing priority to maximize potential revenues for product development, because of shorter timelines and reduced development spending. The focus is mainly on compounds that have some amount of preclinical and human data (e.g., toxicology, PK and/or PD information).

When considering candidates for internal company repurposing, several criteria must be met to justify moving forward. While a strong rationale with supporting data for the target is critical, other factors are important, such as safety data and a reasonable therapeutic index. Financial/strategic concerns can also drive the decision, including IP protection, whether the indication addresses a suitable unmet need and if that need supports a viable commercial opportunity.

Pathways to repurposed products can vary depending on the product and amount of data available for the candidate compounds (61), and some new indications are stumbled upon serendipitously, where observational data, including adverse events/side effects, from clinical studies or approved use, suggest completely unexpected therapeutic uses for “established” products. A classic example here would be the approved use of the anti-angina drug, sildenafil, as a therapy for erectile dysfunction (Table 2).

Similar to the collaborations seen in the NCATS program, pharmaceutical companies have joined with academics to repurpose products. As an example, the Open Innovation Drug Discovery Screening Program from Eli Lilly (62), represents a collaborative approach whereby external research groups can submit compounds for testing in a panel of phenotypic assays representing *in vitro* models of disease.

Similarly, BioMap phenotypic profiling provides high-throughput *in vitro* characterizations for a broad range of human disease models (63), including testing of possible drugs for multiple sclerosis. Examples of a class of products with potential as a radiation MCM are prolyl hydroxylase (PHD) inhibitors, currently in clinical trials for anemia in patients with chronic kidney disease. Because of the known effects of activating HIF-1 α , radioprotection was proposed as a repurposing indication.

In preliminary studies using an irradiated mouse model, it was found that one PHD inhibitor, dimethylallyl glycine (DMOG), improved survival of bone marrow hematopoietic progenitors and inhibited apoptosis in the gut and improved GI function (64). Additional recently published studies suggest that inhibitors of the proteases cathepsin B (65) and DPP-IV (66), or cyclin-d-kinase (CDK) 4/6 inhibitors may

also protect against radiation-induced damage (67). Nonetheless, the reality is that for large pharmaceutical companies, pursuing approvals for indications such as radiation mitigation has limited value due to market size, so many companies have been entering into exploratory private-public partnerships (such as NCATS pre-clinical programs and resources), whereby larger companies can serve “altruistic” goals, helping to develop products for indications that do not necessarily produce the market share needed to drive development.

Session III: New Indications for Generic Products

Unlike patent-protected products, generic products can be produced and sold by multiple companies. A generic product is a pharmaceutical product that is comparable to a patent-protected product in dosage, strength, route of administration quality and intended use. Most generic products enter the marketplace after the existing patent and marketing protection have expired. The lack of existing IP protection, however, can lead to difficulties in incentivizing companies to support the regulatory and other work needed for repurposing of an MCM for a CBRN indication. Below, two main classes of generics with efficacy in radiation injury models are addressed: angiotensin-converting enzyme (ACE) inhibitors and antibiotics. Data available for the radiation indication are presented, alongside a discussion of the challenges involved in their repurposing.

ACE Inhibitors. ACE inhibitors show efficacy in several models of radiation injury, and in multiple organ systems (68). Their use for treating hypertension has generated an enormous safety database, which has extended from pediatric through geriatric patients. There are several ACE inhibitors in clinical use, including lisinopril, enalapril and captopril. Their mechanism of action for hypertension is via inhibition of key components of the renin-angiotensin system (RAS), but ACE inhibitor effects are extended beyond their actions as anti-hypertensives (69), and in a radiation setting may involve activities independent of lowering blood pressure. Researchers have been pursuing the radiation mitigation properties of ACE inhibitors since the late 1980s (70), showing efficacy in kidney (71, 72), lung (73, 74), skin (75, 76) and brain (77, 78), with efficacy linked to RAS modification (79). Current research, done at the Medical College of Wisconsin (Milwaukee, WI), utilizes an irradiated rat model, with a focus on mitigation of lung pneumonitis and fibrosis, as well as renal injury. Using leg-out, partial-body irradiation, administration of lisinopril one week after irradiation improved survival from lung- ($P < 0.01$) and renal- ($P < 0.03$) attributable mortality (74). Earlier reported studies done with enalapril demonstrated a survival benefit ($P < 0.001$) when the drug was administered starting five weeks after 13 Gy WTLI (34), and there is evidence that ACE inhibitors are

effective with growth factors to mitigate late effects in a partial-body shielded model in rats (74). Captopril has also been shown to mitigate increases in breathing rates during pneumonitis (79, 80). In addition, through a collaborative study carried out with Indiana University (Indianapolis, IN), it was demonstrated that lisinopril may be additive with growth factor treatment to improve survival from hematopoietic injury in a lower dose, TBI mouse model (M. Medhora).

Preclinical efficacy that has been observed for ACE inhibitors in the context of radiation injuries has been mirrored in humans given the drug in a radiation setting. Analysis of data from a randomized controlled trial showed that captopril reduced kidney and lung injuries in patients given a bone marrow transplant after TBI (81). In a similar retrospective study, ACE inhibitors reduced the incidence of radiation-induced pneumonitis in patients who received X-ray therapy for lung cancer (33). An ongoing, prospective clinical trial is being conducted through Veterans Affairs (VA, Baltimore, MD and Milwaukee, WI) funding, to study enalapril to reduce the incidence of pneumonitis in patients receiving radiotherapy for thoracic cancers (E. Cohen). Although doses for ACE inhibitors used as anti-hypertensives range from 2.5 to 75 mg/day, the optimum dose for use in the radiation mitigation indication is not known (enalapril is being dosed between 2.5–10 mg/day in the current VA trial). There is potential for additional safety studies and mechanism of action work to be performed in dogs, as ACE inhibitors are in use in canines as a treatment for kidney disease, where they lower angiotensin II and aldosterone levels (82).

Despite the abundant safety data, low cost, wide availability and potential off-label use for these kinds of off-patent drugs, there are few commercial incentives to test and develop them for new indications, and they might be used inappropriately in the absence of solid data for the radiation indication.

There have been challenges in obtaining funds for advanced development of these generic ACE inhibitors for Animal Rule licensure. This has occurred, in part, because of the lack of IP protection, which has made it difficult to find a commercial partner, and the lack of expertise available for product development, regulatory affairs and quality assurance in an academic setting.

To continue to advance these drugs as MCMs, plans are in place to complete ongoing prospective clinical work, as well as to move into large animal models (via U.S. government support) to satisfy the FDA Animal Rule.

Antibiotics. Another class of generic compounds with promise for use as MCMs is antibiotics. One typically understands antibiotics to have a single purpose: the destruction of infectious agents. Often, regardless of the source, antibiotics will be prescribed based on spectrum of action. To truly repurpose an antibiotic, a new indication must be found. For example, if an antibiotic was identified to have antifungal properties (83), or to synergistically

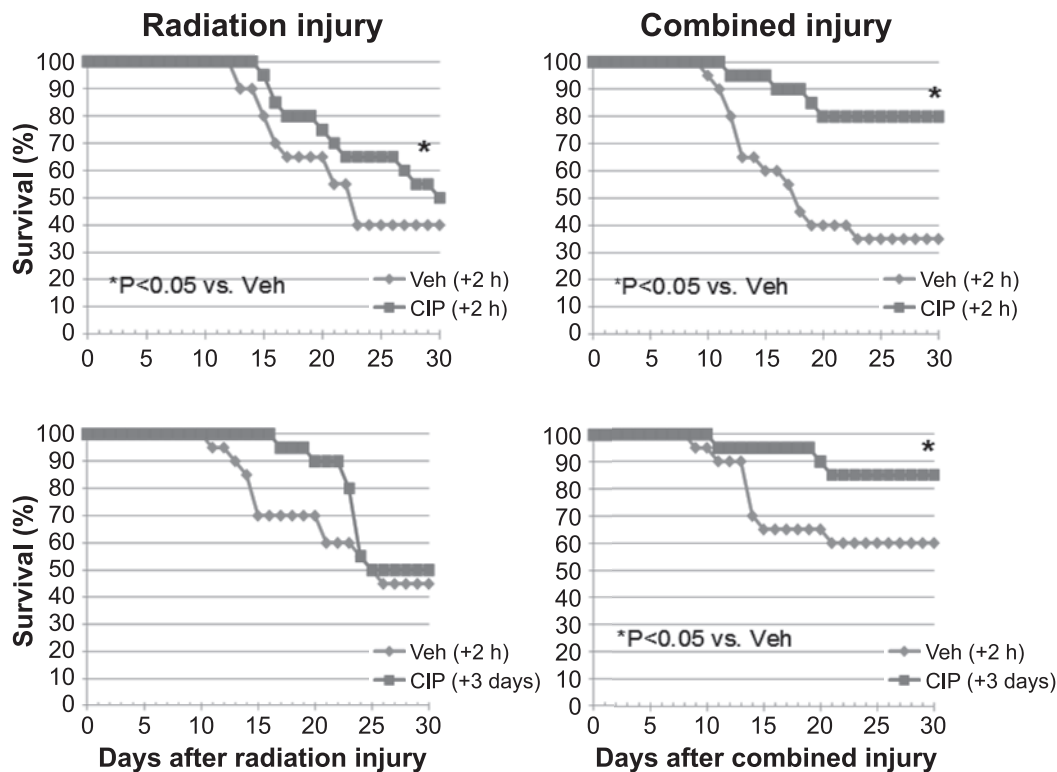


FIG. 1. Efficacy of ciprofloxacin in both radiation only and radiation combined injuries. Ciprofloxacin improves survival after radiation combined injury. Female B6D2F1/J mice (20–25 g; Jackson Laboratory, Bar Harbor, MD) received 9.25 Gy ^{60}Co gamma-photon irradiation (0.4 Gy/min) and/or 15% total-body surface area skin punch wound (panniculus carnosus muscle and overlying skin removed) within 1 h after irradiation. Daily survival rates are shown for radiation injury (left) and combined injury (right) mice treated with ciprofloxacin (CIP, given 90 mg/kg orally, once each day) or vehicle (Veh) starting on day 0. Mice were treated with CIP beginning 2 h (top) or three days (bottom) after wounding. CIP therapy was discontinued on day 21 (22, 106). Figure provided courtesy of Juliann Kiang (AFRRI).

enhance those effects (84), it could be repurposed as an antifungal. Ciprofloxacin is a synthetic chemotherapeutic fluoroquinolone antibiotic, a second-generation drug of the quinolone class of antibiotics, and sold under numerous trade names. It was approved by the FDA for use as an antibiotic in 1987 and is indicated for the treatment of serious infections caused by Gram-negative bacteria such as *Pseudomonas aeruginosa* and *Escherichia coli*. Among the immunomodulatory effects stimulated by quinolones like ciprofloxacin are reduced inflammatory macrophage responses (85), altered cytokine expression patterns (86, 87) and accelerated neutrophil recovery after bone marrow transplant or chemotherapy (88–90).

Radiation combined injury is described as the combination of physical, thermal and/or chemical injury with radiation exposure (<https://bit.ly/2MBvBp3>). In a radiation/nuclear incident, a significant percentage of exposure casualties can be expected to be radiation combined injury patients (91). The primary effect of radiation combined injury is a reduction in LD_{50} compared to radiation exposure alone (92, 93). In work performed at AFRRI in lethally irradiated mice, ciprofloxacin enhanced survival, neutrophil cellularity and functionality after bone marrow transplant (94), and in a high-radiation-dose gastrointestinal (GI)

mouse model, ciprofloxacin diminished or delayed onset of symptoms (95).

In addition, in humans, ciprofloxacin enhanced recovery from hemorrhagic radiation proctitis in radiotherapy patients (96). Therefore, ciprofloxacin, with its ability to comprehensively modulate inflammation, immune signaling and wound healing, represents an obvious mitigator for radiation injuries.

In the radiation combined injury ciprofloxacin efficacy protocol, mice were irradiated and then wounded. Mice were administered ciprofloxacin (90 mg/kg) or vehicle orally, beginning 2 h or three days after wounding, and continued daily for 19 or 22 days (J. Kiang). Ciprofloxacin increased survival in radiation combined injury mice, whether it was initiated 2 h or three days after insult (97) (Fig. 1). Interestingly, with radiation alone, ciprofloxacin delayed onset of mortality, but by 30 days, did not improve survival, suggesting interplay between the effects of ciprofloxacin and the wound healing response mechanism. This survival benefit is specific to ciprofloxacin, as levofloxacin and amoxicillin administrations did not produce similar results (98). These data make a case for the further exploration of repurposing ciprofloxacin for a radiation combined injury indication.

TABLE 4
Guided Discussion Topics

| Technical areas | Regulatory concerns |
|--|--------------------------------|
| Challenges | Special scenarios |
| Bridging data if formulation/route/dose/regimen for new indication differs from licensed product | Market exclusivity |
| Accessing human and/or preclinical data in the context of a product's original indication | Orphan drug designation |
| Shelf-life extensions | Fast-track review |
| Risks to existing indication(s) | Finding of safety and efficacy |
| IP issues and licensing concerns | Biosimilars |
| Selection of appropriate animal models | |
| Benefits | |
| VMI potential | |
| Approved versus off-label use of a product | |
| Potential SNS multi-utility. | |
| Use of approved drug screening libraries | |
| Differences between brand name (patent protected) versus generic product repurposing | |

DISCUSSION

In a NIAID-guided conversation that followed the scientific presentations, meeting participants were asked to comment on several aspects of product repurposing (Table 4). These included technical discussion topics (including a consideration of some of the specific challenges and benefits of repurposing), the use of approved drug screening libraries and how approaches might differ when considering repurposing a patent-protected versus a generic product. Also discussed were regulatory topics that were relevant to repurposing, which included EUAs, the potential for market exclusivity, orphan drug status, fast-track review, findings of safety and efficacy and considerations of biosimilars.

Although several of these topics were brought up during individual presentations and the brief discussions that followed, the formal discussion gave an opportunity for expanded consideration of several areas of importance in repurposing.

Beginning with an overview of the challenges and benefits of repurposing, several discussion topics were considered. First identified and widely-agreed upon as a major challenge was bridging between animals and humans, even for the products considered to be the “low-hanging fruit” (repurposed products). In terms of completed approvals, radiation and infectious disease threats both had obvious products to test, and experienced similar challenges and timeframes in obtaining approval. For example, to support Surfaxin as an MCM, multiple interactions with the FDA were needed to develop bridging approaches, which included characterization of aerosol density, particle size and dose between species.

In addition, bioanalytical assays for products are key and may need to be validated in a new species depending on the animal model employed, or may need to be developed and validated for products that were approved long ago under different regulatory standards. It was agreed that frequent interactions with the FDA are effective and vital to navigating these challenges.

Both BARDA and the NIAID have been pursuing the FDA's process for qualification of drug development tools

such as animal models. For animal models, it is critical that consideration be given regarding what questions to address at the very start of the development process. For example, for radiation there are multiple syndromes possible, and the models need to carefully consider the indications being sought. Total-body irradiation may not accurately model a gut syndrome, and it is unlikely that many people would receive the uniform whole-body irradiation as in the animal models.

Early and continuous discussions with the FDA helped to refine the animal models used in the approval of Neupogen and Neulasta. Fortunately, dating back to a 2004 NIAID-sponsored meeting about NHP models for radiation injuries (99), and sustained investment across the PHEMCE in developing models for radiation injury, there are now several groups with Good Laboratory Practice (GLP) facilities capable of performing adequate and well-controlled studies, along with state-of-the-art irradiators and staff knowledgeable in the FDA Animal Rule. These capabilities were recognized as important factors in developing models to test repurposed products, and animal models that have been used successfully in product approvals provide an excellent starting point.

It is often more challenging for a small pharmaceutical company to repurpose products compared to a large company. This could be due to a limited pipeline of products available for repurposing, insufficient financial resources, and/or lack of regulatory expertise. To address this, several small businesses have approached larger pharmaceutical companies, requesting permission to repurpose products in their portfolio. As mentioned above, Humanetics took this approach. There are potential benefits to both sides of such a relationship; it might be possible for the larger company to also benefit. For example, Congress created the priority review voucher program in 2007, to incentivize development and licensure of products to treat rare diseases (100), and the 21st Century Cures Act, signed into law in December 2016, contains language specific to MCM development (<https://bit.ly/2OXEtqz>). Recent FDA guidance concerning the availability of priority review

vouchers, if a product is first developed and licensed for a CBRN indication, states that "...the FDA is taking steps to quickly and effectively implement the new medical countermeasure priority review voucher program, which aims to incentivize the development of products that can better prepare our nation to respond to emergencies" (101). This draft Guidance for Industry (102) is specific for material threat MCMs, and extends to CBRN products the special requirements and benefits granted to products to treat neglected diseases. Using this advantage, a new product that is first licensed for the radiation indication can benefit the company with another primary clinical indication. For example, vouchers, which are transferrable and allow for priority review by the FDA, could have an estimated sale value in excess of \$100 million dollars (103).

It is also important to note that other U.S. government agencies in addition to HHS are seeking opportunities to repurpose. This interest extends to the DoD (whose mission space is primarily prophylactic MCMs for military populations), as well as the National Aeronautics and Space Administration (NASA), who are seeking MCMs for high-linear energy transfer (LET) radiation exposure. Although MCMs that work for terrestrial/gamma-radiation exposures might not work with high LET, the licensure challenges are similar, and NASA is very interested in repurposing work and MCMs from these areas. For example, NASA is currently looking to incorporate G-CSF for missions; however, issues surrounding shelf-life extension and room temperature storage and stability can be a challenge. NASA also provides funding for MCM development, with 2016 awards focused on funding products with another in-process clinical indication (<https://bit.ly/2vUJbwf>).

BARDA and the NIAID continue to work with both small and large pharmaceutical companies for several indications. In addition, PHEMCE agencies provide expertise and guidance to investigators who work in an academic setting and are new to product development.

For example, within the public/private partnership program, Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator (CARB-X), BARDA has been collaborating with several large biotechnology companies, to fund a pipeline of new broad-spectrum antibiotics (<https://bit.ly/2MgHCTN>). Prior to Amgen's Neupogen licensure, fewer large pharmaceutical companies engaged with the U.S. government; but now that Amgen has shown that industry/U.S. government partnerships can lead to the availability of important products for public health emergency use, more companies are beginning to understand the benefit of being able to reference MCM licensure. As a result, there has been an increase in the number of these groups engaging with the CBRN effort. In addition, there is value added to a company that is involved in repurposing. For example, the NIAID wrote about how companies partnering with the U.S. government can achieve a sustainable radiation business model, in which VMI stock bubbles add to the profit from a licensed product (104).

Several challenges that exist in the generic development space (as opposed to a patent-protected, brand name product) include endgame and partner. In terms of pathway and planning for development, it may be best to seek an ODD (18), since it is typically not possible to obtain a patent. Although an ODD provides for seven years of market exclusivity, questions arise as to whether the U.S. government would be able to sustain total life cycle costs. Identifying a partner to move forward with a label extension is especially problematic for generic products, where there is limited incentive for large pharmaceutical groups to be involved. For many companies, expense is a primary consideration. Therefore, it is incumbent upon the U.S. government to convince companies of the value of working with the U.S. government on the project. This could involve providing incentive funding, and/or assistance on preclinical development and seeking input from the company on the regulatory submissions. This process could represent an insurmountable task for smaller biotech companies, which may not have the resources to move forward.

In many instances, the U.S. government has been the sponsor/holder of an IND. For example, the NIH holds several INDs for different cancer treatments, with investigators encouraged to perform studies under the IND. In other studies, where the NIH supports the clinical trial, the NIH is, as the primary funding source, required to be the IND sponsor [FDA Safety and Innovation Act (FDASIA) §711, 21 CFR §211]. Lastly, when the generic antibiotic ciprofloxacin was approved for anthrax, the DoD conducted the study, worked with the company that held the IP for the drug and provided to the advisory committee. When the advisory committee voted in favor of approval of ciprofloxacin, the FDA published a federal notice, because they had reviewed the data around several products, and stated, via the register notice, that they had made a determination of safety and efficacy (105). It is also important to consider how NCATS efforts to encourage pharmaceutical companies to donate their pipeline products will further accelerate repurposing efforts. Often, waiting until a product is finally approved to seek repurposing is too late, and it is important to have animal models for testing for the new indication already validated to avoid further delays.

CONCLUSION

As demonstrated through the presentations and discussions held during this meeting, repurposing is an important consideration in the development of MCMs. The availability of data from the licensed indication can accelerate licensure of the radiation indication, which would likely be accomplished by label extension, as has already been done with other MCMs for several CBRN threats. The U.S. government will continue to encourage research into these kinds of approaches, and support investigators proposing studies on already-licensed (or nearly licensed) products.

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