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COMMENTARY

Challenges and Benefits of Repurposing Licensed/Approved/Cleared Products for a Radiation Indication

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Increasingly, the risk of a radiological or nuclear public health emergency is a major concern for the U.S. government. To address a potential incident and ensure that the U.S. Government is prepared to respond to any civilian or military casualties that could result, the U.S. Department of Health and Human Services (HHS), together with the Department of Defense, has been charged with the development of medical countermeasures (MCMs) to treat individuals experiencing acute and delayed injuries that can result from exposure to radiation. With limited research and development budgets, and the high costs associated with bringing promising approaches from the bench through advanced product development activities, and ultimately, to regulatory approval, the U.S. Government places a priority on repurposing drugs that have already been commercialized for other indications in humans. To address the benefits and challenges of repurposing licensed products for a radiation indication, the National Institute of Allergy and Infectious Diseases convened a workshop with participants from U.S. Government agencies and industry, as well as academic subject matter experts. Topics included U.S. Government efforts (e.g., funding, regulatory, stockpiling and innovative ways to make drugs available for study), as well as the unique regulatory and other challenges faced when repurposing branded or generic drugs.

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. The mission space for agencies involved in medical countermeasure development is quite broad since radiation can affect multiple organ systems; therefore, resources must be carefully conserved. One way to address this is to investigate products, which are already licensed for other indications, for use in treating radiation injuries.

The concept of repurposing, i.e., identifying a new indication for a drug already licensed for another indication, is not new. Recently, greater emphasis has been placed on the benefits of this approach for MCM development, particularly the reduction in time and cost, since the pharmacology and toxicology have already been extensively studied, and the commercialized drug has developed a well-characterized safety profile (*1–3*). Furthermore, when repurposing for chemical, biological, radiological and nuclear (CBRN) MCMs, developing drugs under the ''Animal Rule'' is certainly less costly than implementing a phase 3 clinical trial. Several drugs have already been repurposed for CBRN injury indications. These include Neupogen® [filgrastim; granulocyte colony stimulating factor (G-CSF)] and Neulasta® [pegfilgrastim; pegylated (PEG) G-CSF] for hematopoietic radiation injuries (both from Amgen Inc., Thousand Oaks, CA),[2] antibiotics for inhalational anthrax (*4*) and pyridostigmine bromide for nerve gas exposure (https://bit.ly/2vXrgp4).

To explore potential benefits and challenges to repurposing licensed products, a workshop sponsored by the National Institute of Allergy and Infectious Diseases (NIAID) was held on August 29, 2017, bringing together participants across multiple U.S. Government agencies [including, within the Department of Health and Human Services (HHS), the National Institutes of Health (NIH), the Food and Drug Administration (FDA) and the

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[2] It should be noted that since the NIAID repurposing meeting, Leukine® (sargramostim, GM-CSF; Partner Therapeutics, Lynnwood, WA), originally indicated for chemotherapy-induced neutropenia, was approved for the treatment of H-ARS in March of 2018.

TABLE 1
Repurposed Drugs and Device

Drug	Manufacturer	Original indication	Date of approval, licensure or clearance	Repurposed indication(s)
Neupogen (filgrastim)	Amgen Inc.	Neutropenia	1991	Licensed for H-ARS in 2015
Neulasta (pegfilgrastim)	Amgen Inc.	Neutropenia	2002	Licensed for H-ARS in 2015
Xigris (*Drotrecogin alfa*; activated protein C)	Eli Lilly and Co.	Sepsis	2002; withdrawn 2011	BARDA-funded for H-ARS
Silverlon (calcium alginate dressing)	Argentum Medical	First- and second-degree burns	Clearance 1998	BARDA-funded for Cutaneous radiation injuries
Mozobil (plerixafor)	AnorMED	Mobilize $CD34^+$ mesenchymal stem cells	2008	NIAID-funded for H-ARS, tissue repair
Surfaxin (lucinactant)	Discovery Labs	Neonatal respiratory distress	2012	NIAID-funded for radiation-induced lung injury
Prinivil® (lisinopril)	Merck & Co. Inc.	Hypertension	1987	NIAID-funded for radiation-induced lung injury
Vasotec® (enalapril)	Merck & Co. Inc.	Hypertension	1981	NIAID-funded for radiation-induced lung injury
Capoten® (captopril)	Bristol-Myers Squibb	Hypertension	1981	NIAID-funded for radiation-induced kidney and lung injury
Ciprofloxacin (fluoroquinolone)	Bayer Corp.	Antibiotic	1987	NIAID-funded for radiation combined injury

Biomedical Advanced Research and Development Authority (BARDA)], as well as from industry and academia, to address the challenges and benefits of repurposing drugs for a radiation indication (full meeting report available online at http://dx.doi.org/10.1667/RR15137.1). The drugs (and device) that were discussed are presented in Table 1. Knowledge gained from prior approvals of radiation-specific drugs was supplemented with approvals from other CBRN mission spaces, as well as examples of industry approaches to repurpose drugs from within their research pipeline. U.S. Government programs aimed at facilitating the availability of drugs for use as MCMs were also discussed.

BACKGROUND

Many U.S. Government agencies collaborate to accelerate research, development and licensure of products for CBRN indications. Within HHS, the NIH focuses on earlier stage research and BARDA focuses on later stage development and procurement of MCMs for the Strategic National Stockpile (SNS). The Centers for Disease Control and Prevention (CDC), with responsibility to provide for storage and distribution of any MCM, and the FDA, with responsibility to assure safety and approve products for use, are critical collaborators in the effort. Interactions among these groups enable the U.S. Government to expedite drug availability during a public health emergency.

In discussing MCMs, a key assumption is that the indication in question is going to be life-threatening, creating ethical challenges for testing the efficacy of the drug in people. To address this, the U.S. FDA published the Animal Efficacy Rule (Animal Rule) in 1999, which applies to testing of products where ''human efficacy studies are not ethical or feasible'' [21 CFR 314.600–314.650 (drugs) or 21 CFR 601.90–601.95 (biologic products)] (*5*), however, safety in humans would still need to be demonstrated prior to regulatory approval. In brief, as with other indications, MCM approval means that the regulatory agency agrees that for a given drug, at a specified strength, in a specified dosage form, for a specified dose, for a specified route of administration, under a specified regimen and for a given indication and usage, the health benefits outweigh the risks. In addition, a drug's intellectual property (IP) status can have a significant impact on the availability of data for the drug's original indication, and the proposed pathway for licensure can depend on whether the drug to be repurposed is still under patent and/or exclusivity protection. Information gaps might need to be addressed to support the new indication; and data, especially human safety data, required to bridge the new indication to the approved product and animal studies may be needed. Any project should start with discussions with the IP holder to determine level of interest, along with early and frequent interactions with the FDA to develop the regulatory strategy.

NIAID, NIH

There are two divisions within the NIAID that are responsible for advancing research and development of MCMs for CBRN indications: the Division of Allergy, Immunology and Transplantation (DAIT) and the Division of Microbiology and Infectious Diseases (DMID). The Radiation and Nuclear Countermeasures Program, within the DAIT, oversees a portfolio of MCMs to treat injury caused by radiation exposure (*6, 7*), and is engaged in

efforts (including funding mechanisms) to repurpose approved drugs with possible efficacy for radiation-induced injuries. Approaches to address biological pathogens are funded through the Office of Biodefense Research Resources and Translational Research, DMID. The office is responsible for the establishment of animal models and reagents for research, as well as services to screen and develop drugs for a wide range of MCM indications under the Animal Rule.

NCATS, NIH

The National Center for Advancing Translational Sciences (NCATS) has a repurposing program focused on investigational products that have been through preclinical development and phase I but have been abandoned or are not yet at the commercialization stage. The aim of this program is twofold: to advance partnerships among industry, government and academia to develop new uses for investigational drugs, with industry identifying assets that are not being pursued; and to foster collaborations for developing these assets. Drugs are publicized on the NCATS website (https://ncats.nih.gov/preclinical/repurpose), along with their mechanism of action, to enable investigators to propose new therapeutic uses.

BARDA, HHS

Through public-private partnerships, BARDA promotes product development, procurement and inventory management of CBRN MCMs. BARDA programs are conducted in collaboration with the CDC and other agencies, and their functions include regulatory approval and management, as well as sustaining the SNS. This includes traditional ''buy and hold'' stockpiling, and vendor- and user-managed inventory.

Centers for Disease Control and Prevention

One of the CDC's roles is to facilitate availability of drugs developed as CBRN MCMs and stockpiled via the SNS. SNS assets include MCMs for approved and off-label indications, as well as unapproved MCMs. The CDC also reviews data for MCM use and advances regulatory filings and emergency use authorizations (EUAs) for the FDA. The EUA is authority given to the commissioner of the FDA to allow for emergency use of unapproved MCMs or off-label use of an approved MCM. EUAs also include shelf-life extension and emergency use instructions (EUIs). EUIs provide guidance to physicians and first responders during an emergency.

In addition to HHS, other U.S. Government agencies are exploring opportunities to repurpose: The DoD funds MCM development primarily for military populations, and the National Aeronautics and Space Administration is seeking MCMs for high-linear energy transfer radiation exposure, a risk of space exploration.

CANDIDATE MEDICAL COUNTERMEASURES AND DISCUSSION

Repurposing Investigational Assets

Interest in identifying new indications for candidate drugs within pharmaceutical companies necessitates a strong rationale with supporting data for the target, including nonclinical and human safety data, therapeutic index, IP protection, the concept of a suitable unmet need and a determination of whether that need supports a viable commercial opportunity. To help identify novel targets or mechanisms for candidate compounds, significant corporate investment has been put into tools such as connectivity mapping, phenotypic screens and mining of existing databases. Establishment of public–private partnerships, such as those enabled by NCATS, provides additional avenues to generate data on potential compounds.

Neupogen® and Neulasta®. The first products approved for hematopoietic acute radiation syndrome (H-ARS) were Amgen's Neupogen and Neulasta, both of which extended their label indications. In 2004, meetings were held between Amgen, NIAID and the FDA to discuss a 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' commercial history, the FDA agreed to licensing via the Animal Rule. Amgen submitted a sBLA to the FDA to use Neupogen in pediatric and adult patients with H-ARS, which was approved in March 2015; Neulasta was subsequently approved for the same indication in November 2015.

Xigris® (activated protein C). Originally FDA approved to treat sepsis, activated protein C (APC) is under study as a radiation mitigator. The ameliorative effects are associated with three mechanisms: activation of clotting factors; protection of the endothelium; and regenerative properties (*8*). In several mouse studies, APC administered after irradiation resulted in enhanced survival over placebo and correlated with higher levels of bone marrow hematopoietic progenitor cells in treated mice (*9*).

Silverlon®. Radiation incidents are expected to result in trauma, thermal burns, ARS and cutaneous radiation injuries, which can damage the basal cell layer of the skin and result in inflammation, erythema and desquamation. Silverlon silver-nylon wound and burn contact dressings are currently stockpiled to treat first- and second-degree burns. The silver ions embedded in the dressing act as an antimicrobial barrier. BARDA is repurposing the existing Silverlon product line for use in public health emergencies.

Mozobil® (plerixafor). Initially approved in 2008, in combination with G-CSF, to mobilize hematopoietic stem cells to the peripheral blood, the drug increases $CD34^+$ cells during apheresis for autologous stem cell transplants (*10*). Mozobil combined with G-CSF is now being considered as a treatment to improve survival in individuals with ARS. The regulatory twist in this narrative is that the company

pursuing the indication is not the IP holder for Mozobil, nor do they currently have an agreement in place with the company holding the IP. The regulatory strategy is to use a 505(b)2 application, which relies on data from studies that they did not conduct nor for which they have right of reference (*11*). There are certain unique requirements, including the identification and execution of studies to fill data gaps for the new indication, a new drug supply, a scientific bridge to the approved product and a patent certification/statement of non-infringement.

Surfaxin®. This surfactant, approved for neonatal respiratory distress syndrome, is also being pursued as a mitigator for radiation-induced lung injury. In a whole-thorax-irradiated mouse model, aerosolized KL4 demonstrated a survival benefit from radiation-induced lung injury (*12*). Because the drug is already approved for use in neonates, a wealth of human safety data, including difficult-to-acquire pediatric patients, is available, increasing the likelihood of approval for a radiation indication.

New Indications for Generic Drugs

Unlike brand name drugs, generic drugs can be produced and sold by multiple companies, provided they are comparable to the branded drug in dosage, strength, route of administration, quality and intended use. The lack of existing IP protection, however, can lead to difficulties in incentivizing companies to support the work needed for repurposing a drug as an MCM. Identifying a partner for a label extension is especially problematic for generic drugs, where there is limited incentive for large pharmaceutical groups; therefore, it becomes incumbent on the U.S. Government to convince companies of the value of moving these drugs forward, perhaps through incentive funding.

Angiotensin converting enzyme (ace) inhibitors. ACE inhibitors are a class of anti-hypertensives with a well-understood mechanism of action and an extensive safety database (*13*) that show efficacy in several models of radiation injury to multiple organ systems (*14*). For example, lisinopril (*15*) and enalapril (*16*) demonstrate a survival benefit even when administered weeks after whole-thorax irradiation in rats, and captopril was shown to reduce kidney and lung injuries in patients given a bone marrow transplant after total-body irradiation (*17*). Despite abundant safety data, low cost and efficacy potential, the lack of IP protection has made it difficult to engage commercial partners to develop this class of drugs for radiation indications.

Ciprofloxacin (Cipro). Cipro is a synthetic chemotherapeutic fluoroquinolone antibiotic that was approved by the FDA for treatment of serious infections caused by Gram-negative bacteria. Cipro has been shown to have immunomodulatory effects, including reduced inflammatory macrophage responses (*18*) and accelerated neutrophil recovery after bone marrow transplant (*19–21*), making it a candidate for repurposing for CBRN MCM indications. In a model of radiation combined injury (a combination of physical, thermal and/or chemical injury with radiation exposure), mice were irradiated and wounded. Cipro-treated animals showed improved survival, whether therapy was initiated 2 h or 3 days after insult (*22*). In humans, Cipro also enhanced recovery from hemorrhagic radiation proctitis in radiotherapy patients (*23*).

CONCLUSION

Repurposing is an important consideration in the development of MCMs for SNS inclusion. Availability of data from the licensed indication can accelerate licensure for the radiation indication, which would likely be accomplished by label extension. This approach has already been successful for other CMRN MCMs. The U.S. government will continue to encourage research into these approaches, and support investigators proposing studies on already-licensed or near-licensed products.

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