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United States' regulatory approved pharmacotherapies for nuclear reactor explosions and anthrax-associated bioterrorism

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Abstract

Introduction: Nuclear reactor incidents and bioterrorism outbreaks are concerning public health disasters. Little is known about US Food and Drug Administration (FDA) approved agents that can mitigate consequences of these events. We review FDA data supporting regulatory approvals of these agents.

Areas covered: We reviewed pharmaceutical products to approved to treat Hematopoietic Acute Radiation Syndrome (H-ARS) and to treat or prevent pulmonary infections following Bacillus anthracis (anthrax) exposure. Four drugs are approved for H-ARS: granulocyte-colony stimulating factor (G-CSF), granulocyte/macrophage colony stimulating factor, pegylated G-CSF, and romiplostim. For bioterrorism-associated anthrax, FDA approved five antibiotics (doxycycline, penicillin-G, levofloxacin, moxifloxacin, and ciprofloxacin), two monoclonal antibodies (obiltoxaximab and raxibacumab), one polyclonal antitoxin (Anthrax Immune Globulin Intravenous) and one vaccine (Anthrax Vaccine Adsorbed). A national stockpile system ensures that communities have ready access to these agents. Our literature search was based on data included in drugs@FDA (2001– 2023).

Expert opinion: Two potential mass public health disasters are aerosolized anthrax dissemination and radiological incidents. Six agents authorized for anthrax emergencies only have FDA approvals for this indication, while for nuclear reactor accidents, four agents have additional regulatory approvals for supportive care for cancer and five have additional FDA approvals as antibiotics for common infections.

Keywords

anthrax; bioterrorism; hematopoietic acute radiation syndrome; stockpile; Animal Rule

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1.0 Introduction

Public health disasters are unpredictable, particularly when they are acts of terrorism. Two potential disasters are nuclear reactor explosions and anthrax-associated bioterrorism. The Food and Drug Agency (FDA) has either approved pharmaceuticals, biologics, and vaccines that may diminish morbidity and mortality of these occurrences or issued regulatory guidances allowing emergency distribution of pharmaceuticals FDA approved previously for other uses. These public health disasters are chronicled by acute events and public health responses, which include catastrophic events in Three Mile Island, Chernobyl, and Fukishama, caustic dust exposure following World Trade Center bombings, chlorine gas exposure following a train crash in [anonymised], and methyl cyanate exposure following an industrial accident at a pesticide plant in India. The number of victims with potential life-threatening complications ranged in the tens of thousands.[1] Although epidemiologic implications of public health emergencies following the nuclear reactor explosion at Chernobyl in 1986 and the bioterrorism outbreak of anthrax in 2001 were addressed, regulatory approval processes or emergency authorizations for pharmacologic therapies for these disasters have not been described.[2]

The objective of this study is to review pathways for FDA approval or Emergency Use Authorization or Centers for Disease Control and Prevention's (CDC) Emergency Use Indication status designation for countermeasure for nuclear reactor accidents or bioterrorism outbreaks from anthrax. We also describe the United States' National Stockpile System (NSS) where several countermeasure drugs, biologics, and antibodies are stored in anticipation of future public health emergencies. The primary data source for this review was clinical information on each FDA-approved therapy that is included in the FDA's website drugs@FDA (2002– 2023).

2.0 Hematopoietic Acute Radiation Syndrome

FDA has approved four drugs (filgrastim (granulocyte colony stimulating factor (G-CSF)), sargramostim (granulocyte macrophage colony stimulating factor (GM-CSF)), pegylated G-CSF, and romiplostim) for treatment of hematopoietic radiation related Hematopoietic Acute Radiation Syndrome (H-ARS), the syndrome that occurred in Chernobyl.

2.1 FDA Approved Drugs for Use in the Setting of Hematopoietic Acute Radiation Syndrome

eIn 2015, FDA approved use of G-CSF to treat H-ARS at a dose of 10 mcg/kg on the basis of safe clinical experience with G-CSF in other FDA approved clinical indications and on efficacy findings in animal studies (under the Animal Efficacy Rule).[3] It is the first FDA-approved medical countermeasure that increases survival in patients exposed to myelosuppressive doses of radiation. Efficacy studies in humans could not be ethically conducted. A randomized blinded placebo-controlled study in non-human primate model (Rhesus macaque) evaluated hematopoietic function from radiation injury following exposure to 7.4 Gy radiation dose (0.8 Gy/minute) followed by subcutaneous injections of G-CSF or placebo. G-CSF reduced 60-day mortality in irradiated non-human

primates (21% vs 59%, p=0.023). G-CSF associated side effects are fever, pain, rash, cough, shortness of breath, headache, and nasal bleeding. The FDA also granted orphan drug designation. FDA submission had been granted priority review that required review of the dossier within 6 months of submission. Although G-CSF was approved by the FDA to treat H-ARS in 2015, in 2013 the Biomedical Advanced Research and Development Authority (BARDA) purchased G-CSF under Project Bioshield for the U.S. Strategic National Stockpile. Between 2013 and 2015, G-CSF use for prevention of hematopoietic toxicity following radiologic or nuclear emergencies would have required FDA designation of Emergency Use Authorization (EUA). G-CSF's initial FDA approval for human use was in 1990, for reduction of the incidence of and duration of neutropenia among cancer patients receiving chemotherapy.

In 2018, FDA approved GM-CSF for H-ARS treatment among adult and pediatric patients.[4] GM-CSF was also approved by the FDA under the Animal Rule. GM-CSF's initial FDA approval for human use had been in 1991 for reduction in incidence and duration of time of neutropenia following chemotherapy in adult patients with acute myeloid leukemia. Most common side effects include fever, injection site reactions, and shortness of breath. A blinded placebo-controlled trial with Rhesus monkeys (n=36 with GM-CSF and n=36 controls) was exposed to total body irradiation at a dose that would be lethal in 50% to 60% of animals by day 60 post irradiation followed by daily subcutaneous injections of sterile water or GM-CSF. GM-CSF treated monkeys had better survival at 60 days (61% versus 17%).[4]

Pegylated G-CSF received FDA approval in 2015 for H-ARS under the Animal Rule based on efficacy studies conducted in animals and data supporting pegylated G-CSF effect on severe neutropenia in patients with cancer receiving myelosuppressive chemotherapy doses. [5] Clinical efficacy was studied in a randomized placebo-controlled non-primate model of radiation injury. Rhesus monkeys were randomized to either control (n=23) or treated (n=23) cohort on study day 1 and day 8 following exposure to total body irradiation of 7.5 Gy delivered at 0.8 Gy/minute (this would be a lethal dose for 50% of the animals). Pegylated G-CSF increased 60-day survival (91% versus 48%, p = 0.014). Pegylated G-CSF received its initial FDA approval for humans in 2002 for reduction in incidence and duration of neutropenia among cancer patients receiving chemotherapy.

In 2021, FDA approved romiplostim for H-ARS to increase survival following exposure to myelosuppressive doses of radiation. Approval was also based on the Animal Efficacy Rule. [6] Using a study of 80 monkeys, romiplostim doubled 60-day survival following exposure to acute radiation injury from 32.5% to 72.5%. Safety was based on safe experience with romiplostim in thousands of humans.

2.2 Chernobyl nuclear reactor explosion- 1986

In 1986, a nuclear reactor accident releasing radioactive isotopes including I-131, Cs-137, Sr-90, and Pu-239 occurred at the Chernobyl Nuclear Power Plant.[7] This accident is considered the worst nuclear power disaster ever. Initial explosions ruptured the reactor. A subsequent fire persisted for days and large amounts of radioactive materials were released.

Exposure to ionizing radiation resulted in life-threatening radiation injury to organs, tissues, cytosols, and cell nuclei.

2.3 Real world experience with H-ARS treatment following radiation accidents

Since 1944, more than 400 radiologic accidents have been registered associated with 3000 substantial radiation exposures and 127 fatalities. In ten accidents since 1996, 30 victims received G-CSF alone or with other growth factors.[8] Twenty-six victims survived. In seven accidents since 1986, 28 victims received GM-CSF alone or with other growth factors. Eighteen victims survived.

2.4 Pharmacoeconomic considerations

Gale and Armitage conclude that given favorable benefit-risk ratios for the 4 agents that have been FDA approved for H-ARS, use of these drugs soon after exposure to acute high-dose whole body ionizing radiation following nuclear terrorism is reasonable.[8] However, there are no cost-effectiveness data available. In 2022, in anticipation of a potential nuclear reactor explosion, President Biden authorized a $290 million purchase of romiplostim to be maintained in the vendor's storage spaces.[9] With the recent introduction of biosimilar formulations of filgrastim, peg-filgrastim, and epoetin, substitution of biosimilars for branded formulations should be considered.

3.0 Bioterrorism and anthrax

Toxic effects occurred after mixing of anthrax spores with body fluids leading to anthrax bacteria activation, multiplication, and spread throughout the body.

3.1 Pharmaceutical considerations

Two monoclonal antitoxin therapies, raxibacumab and obiltoxaximab, and two polyclonal antitoxins, have been developed for prevention and/or treatment of inhalation anthrax. Rather than targeting bacteria, antibodies help eliminate toxins caused by anthrax. These medications are available to physicians through the Centers for Disease Control and Prevention. Although some cases of anthrax respond to antibiotics, advanced inhalation anthrax may not. With later disease stages, bacteria produce more toxins than drugs can eliminate. This provided rationale for development for of the monoclonal antibodies.

In 2012, the FDA approved raxibacumab to treat inhalational anthrax. FDA granted raxibacumab fast track designation, priority review, and orphan product designation.[10] Raxibacumab's effectiveness was based on FDA's review of animal studies under FDA's Animal Efficacy Rule. Studies evaluated a monkey model (one study) or a rabbit model (two studies) compared with placebo. Another study evaluated raxibacumab in combination with an antibacterial drug versus antibacterial drug alone. Animals were challenged with B anthracis spores at 200 x LD-50 to achieve 100% mortality if untreated. Overall, 64% of animals in the monkey study and 44% of animals in one rabbit study receiving a 40 mg/kg dose of raxibacumab survived. Efficacy of raxibacumab and levofloxacin was shown when 82% of New Zealand White rabbits survived 35 days the same anthrax dose administered in single agent studies versus 65% of the rabbits treated with levofloxacin alone (p=0.09).

Safety was evaluated in three pre-approval trials evaluating 326 raxibacumab-treated healthy volunteers and one post-approval study evaluating single dose raxibacumab concurrently with three doses of the FDA-approved Anthrax Vaccine Adsorbed among 286 healthy volunteers. In pre-approval trials, four persons had raxibacumab infusions stopped due to hypersensitivity and anaphylaxis. In the post-approval trial, six persons had raxibacumab infusion stopped due to hypersensitivity and/or anaphylaxis. Rash occurred in 2.8% of healthy persons.

The second monoclonal antibody, obiltoxaximab (a chimeric IgG1 (k)), was licensed in 2016 under FDA's Animal Rule for prevention of inhalational anthrax-associated pulmonary disease at 16 mg/kg body weight intravenously administered as a single dose.[11] In efficacy studies, obiltoxaximab improved survival among animals with inhalational anthrax. Clinical safety was evaluated among 320 healthy subjects treated with one or more 16 mg/kg intravenous doses. Study 1 was a placebo-controlled single dose study (210 patients received obiltoxaximab and 70 patients received placebo). Study 2 was a repeat dose study with 70 patients receiving a first dose and 34 and 31 patients receiving drug in sequences. Study 3 was a drug interaction study with one dose of obiltoxaximab with ciprofloxacin orally for 9 days or a single dose of obiltoxaximab. Hypersensitivity leading to obiltoxaximab discontinuation occurred in 2.5% of patients. Other adverse reactions occurring at >1.5% were mild and responded to diphenhydramine- and included headache (16%), cough (8%), rash (7%), pruritis (4%), rhinorrhea (3%), and infusion site erythema (4%). Antibody evaluation did not identify a single instance of neutralizing antibody. In 2018, FDA approved obiltoxaximab for a second anthrax-inhalation-related indication- to treat inhalational anthrax in combination with one of two commercially available antibiotics-doxycycline or ciprofloxacin.[12] The Animal Rule was also used. Safety was evaluated among 320 healthy volunteers. Most frequent side effects were headache, pruritis, urinary tract infections, cough, nasal congestion, hives, bruising, swelling, and infusion site pains.

Anthrax Vaccine Adsorbed was approved by the FDA in 1970 for pre-exposure prophylaxis in 1970 and, in 2015, under "the Animal Rule" for post-exposure prophylaxis of disease following suspected or confirmed Bacillus anthracis exposure (three-dose regimen), when administered in conjunction with recommended antibacterial drugs.[13] In 2023, the Anthrax Vaccine Adsorbed and an adjuvant received full FDA approval for use in adults 18 to 65 in conjunction with antibacterial drugs, after suspected or confirmed exposure to Bacillus anthracis (two doses over 14 days). A phase 3 trial in animals measured lot consistency, immunogenicity, and safety following a two-dose schedule. A phase 2 study showed non-interference with antibacterial drugs. It has been licensed since 1970. AVA was the first vaccine ever to receive FDA Emergency Use approval under the Animal Efficacy Rule. Efficacy was based on identification of protective antibody levels in rabbit and monkey studies. A 70% probability of survival in animal models from inhalational anthrax was deemed reasonable to predict benefit in humans. Rabbits treated with AVA and two antibiotics had a survival rate of 70% to 100% versus 23% and 44% in rabbits given antibiotics alone after exposure to B anthracis. Safety was evaluated in a study of 200 healthy volunteers. Most adverse events were tenderness, pain, swelling, and injection site redness.

In 2015, the FDA approved Anthrax Immune Globulin Intravenous to treat patients with inhalational anthrax in combination with one of the antibiotics approved by the FDA for use in this setting.[14] The drug had been purchased under Project Bioshield in 2011 as an experimental drug. The drug has been studied under the Animal Efficacy Rule. Survival ranged from 36% to 70% in the monkey and 26% in rabbits versus 0% to 2% in the control animals. Safety was evaluated in 74 healthy human volunteers with side effects including headache, back pain, nausea, infusion site pain, and swelling.

The FDA has approved five commercially available antibiotics for post-exposure prophylaxis during an emergency involving anthrax (doxycycline, penicillin-G, levofloxacin, moxifloxacin, and ciprofloxacin). These agents were approved under the Animal Efficacy Rule. CDC's Emergency Use Instructions, conducted in collaboration with the FDA, are for dispensing of doxycline and ciprofloxacin for post-exposure prophylaxis of anthrax without a prescription during an anthrax emergency.

3.2 Use of anthrax prophylaxis, treatment, and vaccine therapies

The first Anthrax Vaccine Adsorbed was licensed in 1970 for manufacture by the Michigan Department of Public Health. The production plant and the product line were sold to a private company, Bioport, which continues to be the sole US manufacturer of anthrax vaccines. The product license for Anthrax Vaccine Adsorbed calls for subcutaneous administration of six doses of 0.5 milliliters each at day 0, 2 weeks, 4 weeks, 6 months, 12 months, and annual booster doses. Between 1974 and 1989, an estimated 60,000 doses had been distributed to US workers with occupational exposure to anthrax bacteria or spores. In the late 1990s, Anthrax Vaccine Adsorbed was used primarily to protect military troops from weaponized Bacillus anthracis. At the time of the Gulf War, there were concerns that Iraq had produced weapons with anthrax spores. More than 300,000 doses of Anthrax Vaccine Adsorbed were distributed during Operation Desert Storm, probably to more than 150,000 service members. In 1997, because of concerns about biological weapons, then Secretary of Defense William Cohen began a plan to vaccinate all US service members against anthrax. Immunizations began in March 1998 under the Department of Defense's Anthrax Vaccine Immunization Plan. By late 2001, 522,529 service members had received 2,098,455 Anthrax Vaccine Adsorbed doses. In July 2000, in November 2000, and in June 2001, the Department of Defense slowed the anthrax immunization plan, because of supply limitations from Bioport, focusing only on troops thought to be at greatest risk. In late 2001, scientists concluded that a US military researcher had mailed envelopes with anthrax spores to members of congress (including then Senate Majority Leader Tom Daschle) and to the media (Tom Brokaw of NBC News and a reporter at a Boca Raton media outlet).[15] Five of 22 persons who developed cutaneous or inhalation anthrax died.

Toxic effects occurred after mixing of anthrax spores with body fluids leading to anthrax bacteria activation, multiplication, and spread throughout the body. Following the outbreak, the CDC recommended that 10,000 persons with suspected or confirmed exposure to anthrax should receive 60 days of ciprofloxacin (later doxycycline was recommended because of ciprofloxacin toxicity concerns). Several treated individuals reported adverse drug effects, which became the major reason for treatment discontinuation. The CDC's

Adverse Events Working Group reported in 2012 that overall adherence to antibiotics was 44% (range, 21% to 64%). Potentially serious adverse events were identified based on data collected at 10-day and 30-day follow-up. Of 5,343 persons who reported receiving one or more antibiotic doses, 57% reported adverse events during the first 60 days. Fainting, dizziness, light-headedness or seizures occurred in 18 of 2,446 ciprofloxacin-treated persons. In 2001, the CDC offered persons in high-risk settings (post-offices in Virginia, American Media Inc office in Boca Raton, and the Senate office building) the option of 40 days of antibiotics along with a then unapproved vaccine. Overall, 199 of 1,727 persons in high-risk settings received antibiotics and vaccine.

3.3 Pharmacoeconomics of treatments for a bioterrorism outbreak of anthrax

Current recommendations for US individuals exposed to anthrax following a bioterrorism event, based on CDC recommendations, include treatment of persons suspected of having systemic anthrax being started urgently with intravenous antimicrobial combination therapy with doxycycline and penicillin G, ciprofloxacin, levofloxacin or moxifloxacin; one of the two FDA approved monoclonal antitoxins; drainage of pleural effusions, supportive care, and consideration of adjunctive glucocorticoids.[1] A cost-effectiveness model, originally developed in 2012 before FDA approved several pharmaceuticals against anthrax, estimated an incrementqal cost-effectiveness ratio of $162/quality adjusted life year (QALY) for day 2 initiation and $1,018 for QALY for day 5 initiation of antibiotics.[16] An updated model that includes countermeasure agents that received FDA approval since 2012 has not been reported. Factors other than pharmaceutical costs also have pharmacoeconomic implications. For example, while two monoclonal antibodies, and obiltoxaximab, are FDA approved for prevention of pulmonary disease among persons exposed to anthrax, the shelf life of obiltoxaximab is eight years, while the shelf life of raxibacumab is only five years. Hence, costs of maintaining product that has viable shelf-lives are lower for obiltoxaximab due to the lower need of replacing product less often.

4.0 The National Strategic Stockpile

The National Strategic Stockpile (SNS), an integral aspect of treating a public health emergency, was expanded in 1999 to ensure readiness against terrorism events. (chrome-extension://efaidnbmnnnibpcajpcglclefindmkaj/https://www.congress.gov/105/plaws/publ277/PLAW-105publ277.pdf) The 2001 terrorist attacks prompted federal legislation to improve readiness. A 2002 amendment transferred the SNS from the Department of Health and Human Services to the Department of Homeland Security. In 2016, the First Responder Anthrax Preparedness act was passed. A pilot program included provision of FDA-approved anthrax vaccines that are nearing end of their dates of use at the time these vaccines become available to states for emergency response providers at high risk of anthrax exposure if attacks occur. It is anticipated that these providers would voluntarily consent to such administration. In 2001, the federal government responded to the anthrax crisis and delivered vaccines and medicines for oral prophylaxis to 50 sites in 11 states and Washington DC within 5 hours. The US government may use cost-effectiveness models to facilitate decisions about which agents to physically include in the SNS for countermeasures against anthrax and nuclear reactor accidents. These models would

be based on estimates of clinical efficacy, safety, acquisition costs, and drug shelf-lives. With FDA approvals of biosimilar peg-filgrastrim, epoetin, and filgrastim, cost-effectiveness models are needed to facilitate decisions about which cytokine to include in the SNS. These models would parallel cost-effectiveness models that evaluated use of peg-filgrastim versus filgrastim for prophylaxis against chemotherapy-induced neutropenia.

Another factor the US government must consider is the security of the Active Pharmaceutical Ingredient (API) supply chain.[17,18] The FDA maintains a list of drugs in the SNS for the US that are used as medical countermeasures against biological threats, chemical threats, influenza, and radiation threats. For APIs for the 14 drugs that are in the biological threat category (which includes anthrax), the US has 19 API facilities, China has 37 facilities, and the rest of the world has 177 facilities. For APIs for radiation threats (which includes nuclear reactor explosions), the US has 13 facilities, China has no facilities, and the rest of the world has 15 facilities.[17,18] With respect to US dependence on non-US sources of APIs, Woodcock reported to Congress in 2019 on the security of the US pharmaceutical supply. She stated that over time the US would have an increasing reliance on non-US sources of APIs and that FDA databases do not facilitate calculations of volumes of APIs from different sources for US-marketed drugs. Going forward, these data would facilitate identifying how secure the supply chain is for drugs used against biological threats and following nuclear reactor explosions.

The SNS has been activated in several emergencies including the World Trade Center bombing and anthrax attacks, floods, hurricanes, and influenza pandemics. Frequent small scale unique countermeasure responses for anthrax and smallpox and routine deployments of jointly related vaccine stocks have been used to fulfill Department of Defense requirements. In 2022, the federal government expanded and enhanced SNS capabilities to respond to nationwide emerging infectious diseases.

5.0 Conclusion

By 2023, FDA-approval has been granted for five drugs for H-ARS and five antibiotics, two monoclonal antibodies, two polyclonal antitoxins, and two vaccines for bioterrorism-associated anthrax. For several of these agents, clinical effectiveness data are limited to information obtained from experiments with animals and FDA approval was granted under the Animal Rule guidelines. For Anthrax Vaccine Adsorbed and antibiotics identified as countermeasures against anthrax as well as biologics designated for countermeasures against nuclear reactor accidents, extensive safety and efficacy data are available from clinical trials and post-marketing experiences in settings other than nuclear reactor explosions and anthrax outbreaks as well as from observations that have been made following prior episodes of nuclear reactor explosions or a bioterrorism experience with anthrax. In April 2023, the FDA released a draft guidance to facilitate additional drugs to treat H-ARS.[19]

The guidance notes that future drugs will likely receive FDA approval under the Animal Rule. The Guidance notes that each of the currently approved drugs approved for H-ARS received FDA approval on the basis of a single animal-efficacy study in a single non-human primate model of H-ARS to provide substantial evidence of effectiveness, estimates of

treatment effects, and to facilitate establishing of a dose and regimen for human. The adequate and well-controlled animal efficacy studies demonstrated an increase survival at a pre-specified time point post-treatment accompanied by supportive evidence of expected pharmacological effects. Also, results of human efficacy data from relevant FDA approved indications supported the FDA approvals.

6.0 Expert Opinion

Anthrax bioterrorism and nuclear reactor explosions are potentially important public health disasters. The route to FDA approval of pharmacologic countermeasures for these emergencies has improved since 2000. The Animal Rule facilitated FDA approval for two antitoxin therapies, raxibacumab and obiltoxaximab, and one polyclonal antitoxin, that were developed for treatment of inhalation anthrax. Rather than targeting bacteria, these antibodies help eliminate toxins caused by anthrax.

A key consideration is that the National Stockpile has been expanded to include countermeasure treatments for either emergency as well as for other possible public health disasters. SNS personnel can deliver pharmaceuticals for these two emergencies to people who need it anywhere in the US within 12 hours. Foreign countries maintain similar stockpiles, although less is known about these stockpiles, how agents are maintained in up-to-date settings, and how quickly they can be distributed.

Ready access to FDA-approved agents included in the SNS is essential. SNS locations are classified by the US government, but the overall goal is to quickly guarantee appropriate resources to first exposed individuals. The SNS must be consistently available and maintained cost-effectively. Agents that are readily commercially available for H-ARS and antibiotics for an anthrax outbreak are not physically contained in the SNS. These agents are overstocked in certain geographic areas to facilitate distribution. However, FDA approved agents that are not antibiotics that are approved for an anthrax outbreak are physically stored at multiple undisclosed locations. Within these stockpiles, storage of agents with the longest half-lives is optimal. Future development will focus on producing longer half-life materials or extending half-lives of current FDA approved agents. Cost-effectiveness estimates are needed to assist decision-making related to which agents are optimal for inclusion in the national stockpile initiative.

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Declaration of interests

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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Article highlights:

- Public health emergencies involving bioterrorism or nuclear reactors may occur in the United States in the future.
- The Food and Drug Administration (FDA) has approved several therapies under the Animal Rule.
- For four drugs or biologics and one vaccine, data on safety are obtained from healthy volunteers, while efficacy studies are based on evaluations of animals for two monoclonal antibodies and one polyclonal antitoxin.
- For nine commercially available drugs or biologics, FDA approval was based on extensive findings for safety in humans and on efficacy in humans based on human experiences with the 2001 anthrax outbreak and for several clinical observational studies carried out in prior nuclear reaction accidents.
- A national stockpile system ensures that these agents are readily available in case a public health emergency related to bioterrorism or a nuclear reactor explosion occurs. Data on costs, cost-effectiveness, and practical considerations such as shelf-life of these agents are needed.