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June 2022

PUBLIC HEALTH PREPAREDNESS

Medical Countermeasure Development for Certain Serious or Life-threatening Conditions

GAO-22-105248

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GAO Highlights

Highlights of GAO-22-105248, a report to congressional committees

Why GAO Did This Study

Past bioterrorist attacks, such as the anthrax attacks of 2001, highlight the threat of widespread illness and death posed by CBRN agents and the importance of medical countermeasures. GAO has previously reported on the challenges of developing medical countermeasures. Medical countermeasures may need to be developed and approved under FDA's Animal Rule.

The Pandemic and All-Hazards Preparedness and Advancing Innovation Act of 2019 included a provision for GAO to review medical countermeasure development under the Animal Rule. In this report GAO describes (1) FDA efforts to support medical countermeasure developers under the Animal Rule, and (2) the extent of animal model qualification under FDA's Animal Model Qualification Program, and the effect of qualified models on medical countermeasure development.

GAO reviewed FDA documentation, including agency medical countermeasure development guidance. GAO also interviewed or obtained written responses from FDA officials; other federal agencies involved in medical countermeasure development; and a nongeneralizable selection of six developers, three contract research organizations and four academic research and policy organizations. GAO selected interviewees based on their involvement in or knowledge of medical countermeasure development under the Animal Rule.

HHS and the Department of Defense provided technical comments, which GAO incorporated as appropriate.

View GAO-22-105248. For more information, contact Mary Denigan-Macauley at (202) 512-7114 or DeniganMacauleyM@gao.gov.

What GAO Found

The Department of Health and Human Services' (HHS) Food and Drug Administration (FDA) established the Animal Rule in 2002 to allow for the approval of medical countermeasures based on animal efficacy studies when human clinical trials are not ethical or feasible. Medical countermeasures are medical products that may be used to prevent, treat, or mitigate potential health effects of exposure to chemical, biological, radiological, and nuclear (CBRN) agents. GAO found that FDA has undertaken efforts to provide information and feedback to developers to support medical countermeasure development under the Animal Rule. For example, in 2015 FDA issued guidance clarifying the types of studies and data needed to demonstrate product efficacy. FDA has approved 16 medical countermeasures under the Animal Rule, 14 of which were approved over the past decade.

Research of Biological Agents in a Clinical Laboratory

Source: Centers for Disease Control and Prevention. | GAO-22-105248

FDA established the Animal Model Qualification Program in 2011 to provide publicly available animal models to support efficacy testing under the Animal Rule for multiple medical countermeasures for a given disease or condition. Researchers and developers can submit models to the program for qualification, and, once qualified, a model can be used by other developers when appropriate. For example, an animal model for inhalation anthrax would include protocols, such as exposure timing and dosage, to produce disease manifestations that adequately reflect inhalation anthrax manifestations in humans. As of April 2022, FDA has qualified one animal model under the program. FDA officials and many developers GAO spoke with attributed the limited number of qualified models to a lack of an incentive to pursue qualification. Specifically, submitting a model for qualification is voluntary, and FDA officials said the qualification process is rigorous and resource intensive, which may deter submissions. However, many developers reported that the limited number of qualified animal models has not impeded product development, citing other ways to identify animal models that can be used for product development. FDA officials and others that GAO spoke with, including some developers and contract research organizations, said the program may still be beneficial. For example, FDA officials said the program could help further future development of medical countermeasures, particularly for CBRN agents that currently do not have approved medical countermeasures.

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Abbreviations

ASPR	Office of the Assistant Secretary for Preparedness and Response
BARDA	Biomedical Advanced Research and Development Authority
CBRN	chemical, biological, radiological, and nuclear
DOD	Department of Defense
FDA	Food and Drug Administration
HHS	Department of Health and Human Services
NIH	National Institutes of Health

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June 16, 2022

The Honorable Patty Murray
Chair
The Honorable Richard Burr
Ranking Member
Committee on Health, Education, Labor and Pensions
United States Senate

The Honorable Frank Pallone, Jr.
Chair
The Honorable Cathy McMorris Rodgers
Republican Leader
Committee on Energy and Commerce
House of Representatives

Recent experiences with emerging infectious diseases as well as concerns regarding past bioterrorist attacks, such as the anthrax attacks of 2001, highlight the threat of widespread illness and death posed by chemical, biological, radiological, and nuclear (CBRN) agents.[1] These threats underscore the importance of medical countermeasures—medical products, including drugs and biologics such as vaccines—that may be used to treat, prevent, or mitigate potential health effects of exposure to CBRN agents. Medical countermeasure development can be a lengthy, complex, and expensive process. We have previously reported on the challenges and extensive resources required to research, develop, and seek marketing approval for such products.[2]

The Department of Health and Human Services' (HHS) Food and Drug Administration (FDA) typically grants marketing approval for drugs and biologics based on human clinical trials that demonstrate the products are

[1]In September and October 2001, letters laced with anthrax were mailed through the U.S. postal system to two U.S. senators and members of the media.

[2]See GAO, *Public Health Preparedness: HHS Has Taken Some Steps to Implement New Authority to Speed Medical Countermeasure Innovation*, GAO-20-601R (Washington, D.C.: July 29, 2020) and *National Preparedness: HHS Is Monitoring the Progress of Its Medical Countermeasure Efforts but Has Not Provided Previously Recommended Spending Estimates*, GAO-14-90 (Washington, D.C.: Dec. 27, 2013).

safe and effective for their intended use.[3] However, it would be unethical or infeasible to conduct human clinical trials when developing certain medical countermeasures. For example, it would be unethical to expose healthy individuals to harmful CBRN agents, such as cyanide, to conduct human clinical trials for products that treat the disease or condition associated with the CBRN exposure. For such medical countermeasures, FDA issued regulations commonly known as the Animal Rule in 2002. This Rule generally allows FDA to approve a medical countermeasure for serious or life-threatening conditions based on evidence from animal efficacy studies—studies that measure the effectiveness of a product in preventing or treating a condition—if the product is reasonably likely to produce a clinical benefit in humans.[4]

In part due to the complexities and challenges of developing medical countermeasures under the Animal Rule, both FDA and HHS's Biomedical Advanced Research and Development Authority (BARDA) support and advise medical countermeasure product developers (hereafter referred to as developers). For example, FDA often provides feedback to developers developing products under the Animal Rule to help ensure that their animal efficacy studies generate sufficient evidence to support approval under the Animal Rule. BARDA, which funds and helps oversee the advanced research and development of certain medical countermeasures, also advises developers working on products

[3]See 21 U.S.C. § 355(b) (drugs) and 42 U.S.C. § 262(a) (biologics). See also 21 C.F.R. Part 312, Subpart B (investigational new drug applications); § 314.50 (new drug applications); and § 601.2 (biologics license applications) (2021). Drugs are chemically synthesized, while biologics—which include vaccines, blood products, and proteins, among other things—are derived from living sources such as humans, animals, and microorganisms. FDA approves drugs that are safe and effective and licenses biologics that are "safe, pure, and potent," which is widely interpreted to mean safe and effective. For the purposes of this report, we use the term "approve" for both drugs and biologics.

[4]See 67 Fed. Reg. 37988 (May 31, 2002) (codified at 21 C.F.R. Parts 314, Subpart I, and 601, Subpart H (2021)). Only drugs and biologics can be approved under the Animal Rule. Other medical products regulated by FDA, such as medical devices, cannot be approved under the Animal Rule. In order for a product to be approved under the Animal Rule, its safety must be established in humans. While the Animal Rule has predominantly been used for the development of medical countermeasures to address potential public health emergencies, the Animal Rule is not exclusive to medical countermeasures and could be used for other products, such as antitoxins for snake bites, in which human clinical trials may not be ethical or feasible.

While preliminary product studies that explore the potential of a product to have the desired effect are often performed in animals as part of early product development to help provide a basis to proceed to clinical trials in humans, the Animal Rule allows FDA to grant approval for products for use in humans based on animal efficacy studies.

under the Animal Rule. This includes providing feedback on navigating FDA regulatory processes.

FDA also established the Animal Model Qualification Program in 2011 to help facilitate medical countermeasure development under the Animal Rule. The program is intended to provide publicly available information on potentially useful animal models for developers to use during product development and when seeking marketing approval. Animal efficacy studies use animal models—a specific combination of an animal species, specified CBRN agent, and the manner of the agent's exposure in the animal—that reflect key elements of the human experiences with the disease or condition associated with the CBRN exposure. For example, an animal model for inhalation anthrax would include protocols for the timing, delivery method, and dosage of exposure to produce disease manifestations in an animal species that adequately reflect key elements of the disease manifestations of inhalation anthrax in humans.[5] A single, qualified animal model may be used to develop multiple medical countermeasures for a single condition caused by a CBRN agent, potentially streamlining medical countermeasure development.[6] The program is also intended to help developers reduce redundancy and conserve resources.

The Pandemic and All-Hazards Preparedness and Advancing Innovation Act of 2019 includes a provision for us to review and report on medical countermeasure development under the Animal Rule.[7] In this report we describe

1. FDA efforts and information sharing with BARDA to support medical countermeasure developers under the Animal Rule; and
2. the extent to which FDA has qualified animal models under the Animal Model Qualification Program and the effect, if any, of these models on medical countermeasure development under the Animal Rule.

To answer these objectives, we reviewed agency documentation, including FDA product development guidance, meeting minutes, advisory

[5]Exposure to the CBRN agent *Bacillus anthracis* causes the condition of inhalation anthrax.

[6]For the purposes of this report, we use "qualified model" to refer to an animal model qualified through the Animal Model Qualification Program.

[7]Pub. L. No. 116-22, § 604, 133 Stat. 905, 957-58.

committee proceedings, and product approval documentation for products approved under the Animal Rule, and a BARDA contract with a product developer.[8] We also reviewed articles published from 2009 through 2021 on animal models and animal efficacy studies for products approved under the Animal Rule. We interviewed officials from FDA and BARDA, along with other stakeholders. Specifically, we interviewed officials or obtained written responses from the National Institutes of Health (NIH) and the Department of Defense (DOD); six of 10 developers that have had a product approved under the Animal Rule since 2012; three clinical contract research organizations that have conducted animal efficacy studies for approved Animal Rule products; and four academic research and policy organizations with knowledge of medical countermeasure development under the Animal Rule.[9] Among the four remaining developers we were unable to interview, two declined to speak with us, citing issues identifying staff with relevant institutional knowledge, and two were acquired by other companies.[10] We selected the other stakeholders to interview based on their involvement in or knowledge of medical countermeasure development under the Animal Rule (for additional information on our interview selection, see app. I). What we found through our interviews with developers, contract research organizations, and academic research and policy organizations is not generalizable to all such developers and organizations; however, the interviews provide insight into the development of animal models and medical countermeasures under the Animal Rule.

[8]Advisory committees provide independent advice and recommendations to FDA on scientific and technical matters related to the development and evaluation of products regulated by the agency.

[9]NIH's National Institute of Allergy and Infectious Diseases, along with DOD's Joint Program Executive Office for Chemical, Biological, Radiological and Nuclear Defense and Defense Threat Reduction Agency are involved in and have conducted medical countermeasure research and product development related to the Animal Rule, including having conducted work to develop animal models for CBRN agents.

We obtained written responses from NIH and one developer.

[10]We focused our interviews on developers that developed medical countermeasures after implementation of the Animal Rule. Two medical countermeasures, pyridostigmine bromide and Cyanokit, were approved under the Animal Rule prior to 2012 but had been developed before the Animal Rule's implementation. Pyridostigmine bromide was used during the Persian Gulf War in 1990 and 1991 as a pretreatment for nerve agents, and the active pharmaceutical ingredient in Cyanokit received marketing approval in France in 1996 for cyanide exposure.

As part of our work, we examined FDA and BARDA efforts to share information to help develop medical countermeasures under the Animal Rule in the context of federal internal control standards.[11] We determined that the information and communication component was significant to our objective, including the underlying principle that management should externally communicate necessary information to achieve the agency's objectives.

We conducted this performance audit from May 2021 to June 2022 in accordance with generally accepted government auditing standards. Those standards require that we plan and perform the audit to obtain sufficient, appropriate evidence to provide a reasonable basis for our findings and conclusions based on our audit objectives. We believe that the evidence obtained provides a reasonable basis for our findings and conclusions based on our audit objectives.

Background

HHS Offices and Agencies Involved with Medical Countermeasure Development under the Animal Rule

HHS offices and agencies are responsible for helping to develop and oversee medical countermeasures to address CBRN threats. This responsibility involves a range of activities, from prioritizing and supporting the development of medical countermeasures to addressing identified CBRN threats, reviewing and granting marketing approval for medical countermeasures, and stockpiling medical countermeasures for use in public health emergencies. In January 2022, we placed HHS's leadership and coordination of public health emergencies on our high risk list in part due to concerns related to the stockpiling and management of medical countermeasures.[12]

HHS offices and agencies support the development of medical countermeasures to address CBRN threats in part by engaging with and providing research and development support to developers. Several offices and agencies within HHS have specific responsibilities for public health preparedness and response activities related to furthering the

[11]Internal control is a process effected by an entity's oversight body, management, and other personnel that provides reasonable assurance that the objectives of an entity will be achieved. GAO, *Standards for Internal Control in the Federal Government*, GAO-14-704G (Washington, D.C.: Sept. 10, 2014).

[12]GAO, *COVID-19: Significant Improvements Are Needed for Overseeing Relief Funds and Leading Responses to Public Health Emergencies*, GAO-22-105291 (Washington, D.C.: Jan. 27, 2022).

development of medical countermeasures, including those developed under the Animal Rule (see fig. 1).

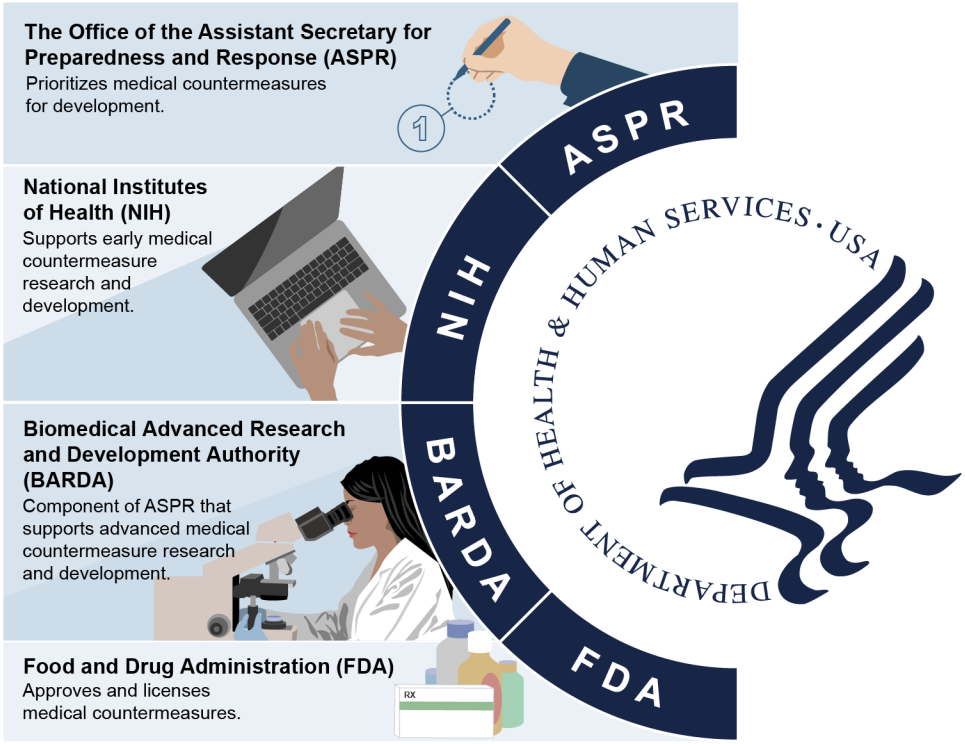
- **The Office of the Assistant Secretary for Preparedness and Response (ASPR).** This office leads the federal medical and public health response to public health emergencies, including prioritizing medical countermeasures for development.[13]
- **NIH.** This agency conducts and funds early development research that can be used for medical countermeasure development. For example, NIH conducts research to better understand CBRN agents and human and animal responses to the agents. NIH's National Institute of Allergy and Infectious Diseases supports the development of animal models that can be used for medical countermeasure development.
- **BARDA.** As a component of ASPR, BARDA oversees the advanced research and development of certain medical countermeasures for CBRN threats. BARDA contracts with and funds the work of developers developing products under the Animal Rule and often provides product development feedback based on BARDA officials' product development and regulatory expertise. In addition, BARDA contracts with clinical contract research organizations that provide technical support for developers. BARDA also works with contract research organizations to develop animal models that can be used to help develop medical countermeasures under the Animal Rule. These contract research organizations have specialized laboratory facilities and trained staff to execute animal efficacy studies under the Animal Rule. While BARDA provides financial and technical support to developers, BARDA does not have any regulatory authority to approve medical countermeasures for marketing in the United States.[14]
- **FDA.** As part of its overall role to assess the safety and effectiveness of medical products, this agency ensures and assesses the safety and effectiveness of medical countermeasures by regulating their development, granting marketing approval, and conducting postmarket surveillance. FDA also provides technical assistance to

[13]ASPR is also responsible for managing the Strategic National Stockpile, the repository for drugs, biologics, medical devices, and other supplies, for use in a bioterrorist attack or other public health emergency.

[14]Although a component within ASPR, we refer to BARDA as an agency throughout this report.

developers to help ensure that their product development meets FDA's regulatory requirements and supports the development of product development tools, such as animal models that can be used to develop products under the Animal Rule.[15]

Figure 1: Highlighted Responsibilities for Medical Countermeasure Development, by HHS Office or Agency



Source: GAO analysis of Department of Health and Human Services (HHS) information. | GAO-22-105248

FDA Review and Approval of Medical Countermeasures under the Animal Rule

The Animal Rule includes four key requirements that must be met for FDA to approve a product under the Animal Rule.

[15]These HHS offices and agencies, along with other federal agencies and departments, such as DOD, are partners in HHS's federal interagency decision-making body, the Public Health Emergency Medical Countermeasures Enterprise, which, among other responsibilities, provides recommendations to the Secretary of Health and Human Services regarding CBRN medical countermeasure research, development, and procurement. See 42 U.S.C. § 300hh-10a.

1. The mechanism of toxicity of the CBRN agent (i.e., how it causes the disease or condition) and the product's mechanism of action (i.e., how the product produces its effect to prevent or treat the disease or condition caused by the CBRN agent) are reasonably well understood.
2. The product's effect is demonstrated using animal models for more than one animal species expected to react with a response that is predictive for humans (unless the effect is demonstrated in a single animal species that represents a sufficiently well-characterized animal model for predicting the response in humans).[16]
3. The animal study outcome is clearly related to a desired benefit in humans, such as in the enhancement of survival.
4. The data or information allows for the selection of an effective dose in humans.[17]

There are several additional requirements a medical countermeasure must meet to obtain approval under the Animal Rule, including that medical countermeasures developed under the Animal Rule need to demonstrate that they are safe for their intended human use.[18] The Animal Rule also requires developers to submit plans for conducting human studies after product approval, in the event that individuals are exposed to the CBRN agent and develop associated conditions that the product is intended to prevent or treat. The purpose of these human studies is to verify the medical countermeasure's safety and effectiveness

FDA Human Clinical Trials

Typically, before drug developers may apply to FDA for approval to market a drug or biologic in the United States, they must conduct human clinical trials to test the safety and efficacy of their products. Generally, in clinical trials, one group of trial participants—the experimental group—is given the product, while a separate control group does not receive the product. The clinical trials follow a typical series from early, small-scale studies to late-stage, large-scale studies. The data and outcomes associated with the experimental and control groups are compared with one another to determine whether the product achieves its intended effect, and to assess any potential safety risks.

Source: Food and Drug Administration (FDA) (information, photo). | GAO-22-105248

[16]A "sufficiently well-characterized animal model" means the model has been adequately evaluated for its responsiveness for predicting and reflecting the key elements of the human experiences with the disease or condition associated with the CBRN exposure.

[17]In assessing the sufficiency of animal data for product approval, FDA may also take into account other data, including human data, available to the agency. For example, some products developed under the Animal Rule had been previously approved for other, relevant non-countermeasure indications and had available relevant data from prior human clinical trials.

[18]There are no product safety requirements particular to the Animal Rule. Developers seeking product approval under the Animal Rule need to provide appropriate safety data and information similar to drugs and biologics developed outside the Animal Rule, such as data from human clinical trials.

when used in humans who have been exposed to the CBRN agent, when such studies are feasible and ethical.[19]

As of April 2022, FDA had approved 16 medical countermeasures under the Animal Rule. See table 1.

Table 1: Products Approved by FDA under the Animal Rule as of April 2022

Product (proprietary name)	Developer[a]	Indication[b]	FDA approval year	BARDA-funded
Pyridostigmine bromide	U.S. Army	Soman nerve agent poisoning	2003	No[c]
Cyanokit	EMD Pharmaceuticals	Cyanide poisoning	2006	No[c]
Levaquin	Janssen	Plague	2012	No
Raxibacumab	Human Genome Sciences	Anthrax	2012	Yes
BAT	Cangene	Botulism	2013	Yes
Cipro	Bayer Healthcare Pharmaceuticals	Plague	2015	No
Anthrasil	Cangene	Anthrax	2015	Yes
Neupogen	Amgen	Acute radiation exposure	2015	Yes
Avelox	Bayer Healthcare Pharmaceuticals	Plague	2015	No
Neulasta	Amgen	Acute radiation exposure	2015	Yes
BioThrax	Emergent BioSolutions	Anthrax	2015	Yes
Anthim	Elusys Therapeutics	Anthrax	2016	Yes
Leukine	Sanofi-Aventis	Acute radiation exposure	2018	Yes
TPOXX	SIGA Technologies	Smallpox	2018	Yes
Nplate	Amgen	Acute radiation exposure	2021	Yes
Tembexa	Chimerix	Smallpox	2021	Yes

Source: GAO analysis of Food and Drug Administration (FDA) and Biomedical Advanced Research and Development Authority (BARDA) documentation. | GAO-22-105248

[a]Refers to the original entity that submitted the medical countermeasure for FDA approval under the Animal Rule. For several products, the developer listed has since been acquired by another company or has transferred the rights to the product to another company.

[b]The indication generally describes the disease, condition, or symptoms that the product is intended to treat, prevent, or mitigate. The indications listed in the table are abbreviated references to more specific and detailed indications.

[19]In addition, products approved under the Animal Rule are required to include patient labeling that explains product approval was based on efficacy studies conducted in animals alone, and products may also be subject to postmarketing restrictions to ensure safe use. See 21 C.F.R. §§ 314.610(b)(2) and (3) and 601.91(b)(2) and (3) (2021).

[c]Products approved by FDA prior to BARDA's establishment in December 2006.

Animal Model Qualification Program

FDA established the Animal Model Qualification Program to provide publicly available animal models to support efficacy testing for multiple products under the Animal Rule for a given disease or condition caused by a CBRN exposure.[20] Under the program, FDA may qualify an animal model for a specific context of use if the agency determines that the model reflects key elements of the human experiences with the relevant disease or condition associated with the CBRN exposure and is appropriate for use in animal efficacy studies. For example, if FDA qualified a particular animal model for the treatment of pneumonic plague through the Animal Model Qualification Program, developers could use the qualified model to develop and test multiple medical countermeasures for pneumonic plague under the Animal Rule instead of developing their own models, if the model was appropriate for use in testing the specific medical countermeasures.

When a developer uses a qualified animal model within its stated context of use, FDA does not have to reevaluate the appropriateness of the model as a model of key elements of the human disease or condition, but it will still need to evaluate the model for its appropriate use with the product. For example, if a developer working on a pneumonic plague product uses a qualified animal model within its stated context of use, FDA would not have to reevaluate the appropriateness of the model's use in efficacy studies for the product.

Other federal agencies involved in developing animal models, such as NIH, BARDA, or DOD, along with academic researchers and developers, can submit models for qualification under the Animal Model Qualification Program. While developers need to use animal models that are expected to be predictive for humans for their animal efficacy studies to have their products approved, submitting a model for qualification under the Animal Model Qualification Program is voluntary—the use of a qualified model is not needed to obtain product approval under the Animal Rule.[21]

[20]Information on qualified animal models is available on FDA's website. See Food and Drug Administration, *CDER & CBER Drug Development Tool Qualification Project Search*, accessed April 25, 2022, https://fda.force.com/ddt/s/.

[21]FDA officials told us they do not have any staff solely dedicated to the Animal Model Qualification Program and do not have funding data specific to the program.

FDA Efforts and Information Sharing with BARDA to Support Medical Countermeasure Developers under the Animal Rule

FDA Support for Medical Countermeasure Developers under the Animal Rule

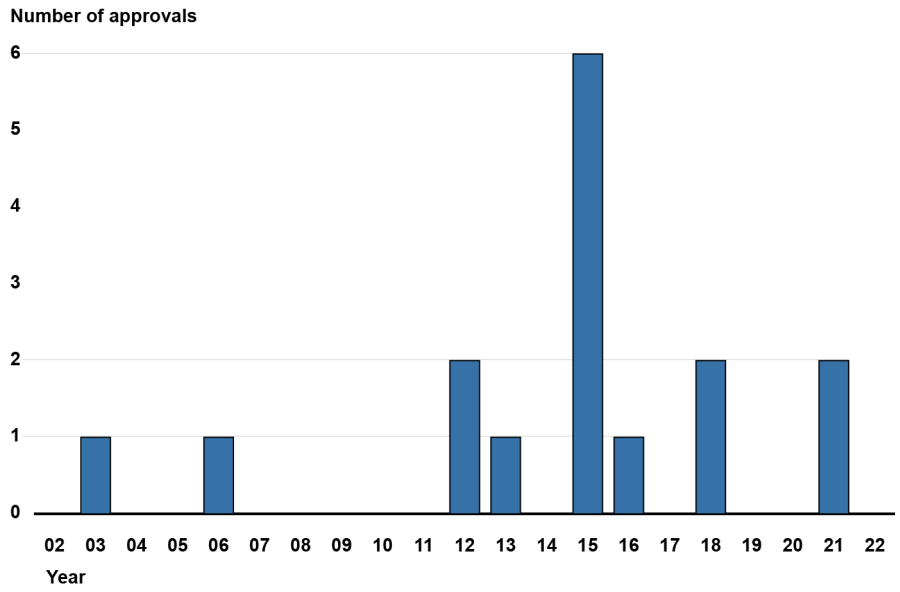
Based on our review of agency documentation and interviews with agency officials and stakeholders, we found that FDA undertook efforts to support the development of products under the Animal Rule. These efforts included issuing clarifying guidance and sharing other information to help developers through the approval process. NIH and DOD officials, developers, clinical research organizations, and academic research and policy organizations we interviewed told us that these efforts helped further the development of medical countermeasures. In particular, these stakeholders said that the following FDA practices helped further the development of medical countermeasures under the Animal Rule.

- **Ongoing engagement and feedback.** Many developers and academic research and policy organizations reported that FDA had constructive, ongoing communication with developers to provide input and feedback on animal models, animal efficacy study designs, and preliminary results. For example, one developer noted that FDA helped identify the appropriate animal models to use for its product efficacy studies and provided input on the dosing protocols for the CBRN agent. FDA officials noted that early engagement with developers to obtain consensus on animal models is particularly important before initiating the animal efficacy studies.
- **FDA advisory committee meetings.** Many developers, contract research organizations, and a policy organization cited FDA advisory committee meetings as helpful in furthering medical countermeasure development. These stakeholders told us the meetings helped bring forward useful external expert perspectives and helped to generate consensus on animal efficacy study designs. For example, one developer noted that an advisory committee helped generate scientific consensus on relevant animal models to use for animal efficacy studies for a given CBRN agent.

Some stakeholders attributed recent positive experiences with medical countermeasure development under the Animal Rule in part to FDA addressing challenges in the years after the Animal Rule's implementation in 2002. According to BARDA and DOD officials, developers, and academic research and policy organizations, during the early years of the Animal Rule's implementation, there was limited data and information on how to best use animal studies to demonstrate efficacy. According to these stakeholders, FDA's initial expectations for conducting studies were not clear. In addition, these stakeholders explained that, because few products had yet been approved under the Animal Rule, there were limited precedents regarding the level of data and information required by FDA to demonstrate efficacy for approval.

FDA, BARDA, and DOD officials, developers, and academic research and policy organizations generally described the initial challenges with the Animal Rule as early program "growing pains." These stakeholders told us that, over the past decade as FDA approved more medical countermeasures under the Animal Rule, the agency clarified the types and nature of animal efficacy studies and data needed to demonstrate efficacy under the Animal Rule (see fig. 2). In particular, the approvals established precedents that clarified product approval requirements and helped guide later development. For example, one developer we spoke with noted that it used product approval information from a previously approved medical countermeasure to inform its approach to seeking product approval for its product.

Figure 2: FDA Animal Rule Product Approvals by Year



Source: GAO analysis of Food and Drug Administration (FDA) documentation. | GAO-22-105248

In addition, NIH and DOD officials and a developer told us FDA guidance issued in 2015 on the Animal Rule helped better define the agency's expectations for conducting animal efficacy studies under the Rule.[22] To help ensure developers understand how to meet the Animal Rule's requirements, the guidance describes the essential elements of an appropriate animal model and animal efficacy study design considerations for generating sufficient evidence of product efficacy, and includes product review checklists for developers.[23] DOD officials noted that additional CBRN-specific guidance has also helped provide clarity on FDA's expectations. For example, FDA issued guidance on developing products under the Animal Rule for the treatment or prevention of

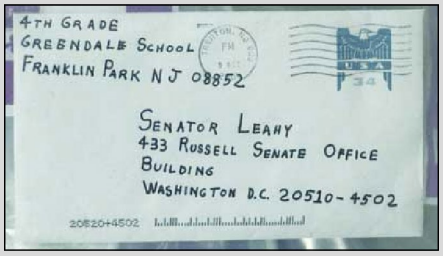
[22]Food and Drug Administration, *Product Development under the Animal Rule Guidance for Industry* (Silver Spring, Md: Oct. 2015). FDA previously issued draft guidance for developing medical countermeasures under the Animal Rule in 2009. We reported in 2011 that medical countermeasure developers faced difficulty in applying the draft guidance, which presented challenges for product development. See GAO, *Public Health Preparedness: Developing and Acquiring Medical Countermeasures against Chemical, Biological, Radiological, and Nuclear Agents*, GAO-11-567T (Washington, D.C.: Apr. 13, 2011).

[23]The guidance also provides information on FDA's expectations about human safety data, among other additional regulatory considerations.

smallpox, which, among other things, provides information on smallpox animal models and smallpox-specific considerations for conducting animal efficacy studies.[24]

Anthrax

The Food and Drug Administration has approved medical countermeasures developed under the Animal Rule for anthrax. Anthrax is a disease caused by bacteria known as Bacillus anthracis that can lead to severe illness in humans. Bacillus anthracis is found naturally in soil, though it can also be used as a biological weapon. In 2001, powdered Bacillus anthracis spores were mailed through the U.S. postal system, leading to five deaths and illness in 17 others.



Letter sent to a U.S. Senator during the 2001 anthrax attacks.

Source: Centers for Disease Control and Prevention (information), Federal Bureau of Investigation (photo). | GAO-22-105248

NIH officials, several developers, and several contract research organizations, also cited the development of animal models for conducting animal efficacy studies under the Animal Rule as having further aided the development of medical countermeasures. According to these stakeholders, early after implementation of the Animal Rule, few animal models that could support medical countermeasure research and development had been developed. Since then, federal agencies, contract research organizations, and developers have invested resources in and worked to study and develop many animal models that have supported medical countermeasure product development. For example, according to NIH officials, there are now small animal and non-human primate animal models that are considered relevant and appropriate for studying a wide range of conditions stemming from CBRN agents, including anthrax, smallpox, plague, tularemia, and conditions associated with acute radiation exposure. (See sidebar for information about anthrax.)

DOD officials, a developer, and an academic research organization noted that it may be more difficult to develop and obtain FDA approval for certain medical countermeasures because of differences in how the products are developed or used. (See fig. 3 for information on the challenges developing medical countermeasures under the Animal Rule.) In particular, they noted that preventive products, such as vaccines, may be more difficult to develop. Such products often involve demonstrating that animal immune responses reflect expected human immune responses, which these stakeholders said may involve greater complexity than demonstrating the efficacy of treatments. In addition, FDA and DOD officials noted that developers of medical countermeasures for prevention and prophylaxis (pretreatment) may have to provide greater evidence of product safety for approval under the Animal Rule. In particular, these products are subject to a different risk-benefit analysis since they would be given to healthy individuals and those not experiencing symptoms

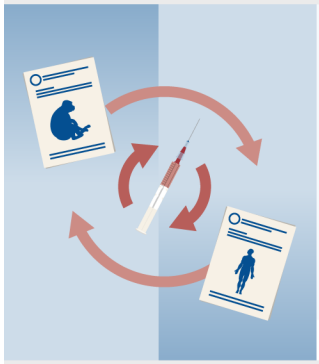
[24]Food and Drug Administration, *Smallpox (Variola Virus) Infection: Developing Drugs for Treatment or Prevention Guidance for Industry* (Silver Spring, Md: Nov. 2019). Other FDA guidance documents for developing products under the Animal Rule include Food and Drug Administration, *Guidance for Industry, Internal Radioactive Contamination — Development of Decorporation Agents* (Rockville, Md: Mar. 2006) and *Anthrax: Developing Drugs for Prophylaxis of Inhalational Anthrax Guidance for Industry*, (Silver Spring, Md: May 2018). FDA plans to issue additional guidance in 2022 on developing medical countermeasures for acute radiation syndrome under the Animal Rule.

from CBRN exposures, as opposed to treatments given to those actively experiencing symptoms.

Figure 3: Challenges Inherent to Developing Medical Countermeasures under the Animal Rule

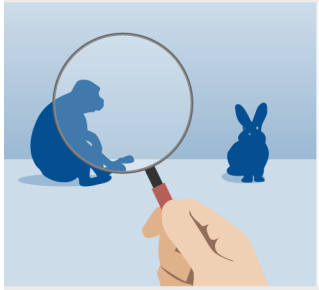
Medical countermeasures are medical products that may be used to prevent, treat, or mitigate potential health effects from exposure to chemical, biological, radiation and nuclear (CBRN) agents. It would be unethical or infeasible to conduct human clinical trials for certain medical countermeasures, and the Animal Rule allows the Food and Drug Administration (FDA) to approve countermeasures based on evidence from animal efficacy studies if the product is reasonably likely to produce a clinical benefit in humans. Federal agency officials, some medical countermeasure developers, and contract research organizations that we spoke with cited a number of challenges inherent to developing countermeasures under the Animal Rule, including the following:

Determining clinical benefit in humans



Several stakeholders told us that the process of developing animal models and conducting animal efficacy studies to establish a reasonable likelihood of clinical benefits in humans is a challenging and often iterative process. For example, for certain diseases and conditions caused by CBRN agents, there may be limited data or information on the condition in humans, thus making it more difficult to develop appropriate animal models in which to test the efficacy of the product and to determine a clinical benefit in humans. Additionally, it may be challenging to extrapolate an effective dose for humans from animal data, as products may act differently in humans, and humans may require a different dosage or a different drug exposure.

The need for studies in more than one animal species



To ensure a product has a reasonable likelihood of a clinical benefit in humans, FDA can require countermeasure developers to demonstrate product efficacy in more than one animal species. Given the difficulties of conducting animal efficacy studies to determine clinical benefits in humans, some stakeholders told us that having to do so for more than one animal species can present challenges to countermeasure development. Of the 16 countermeasures approved under the Animal Rule as of April 2022, eight products demonstrated efficacy in more than one animal species.

Obtaining and caring for animals

Some stakeholders also cited certain challenges with conducting efficacy studies in animals. Certain animal species that are often used for efficacy studies for medical countermeasures developed under the Animal Rule, such as non-human primate species, can be difficult to obtain and care for.

Source: GAO interviews with medical countermeasure development stakeholders. | GAO-22-105248

FDA and BARDA Information Sharing to Support Medical Countermeasure Developers

FDA and BARDA efforts to better share information between one another have helped support developers under the Animal Rule, according to agency officials and some stakeholders.[25] Because both agencies are providing feedback to developers, it is important that the agencies have a shared understanding of the relevant information and issues affecting product development to avoid providing conflicting or misaligned feedback. According to FDA and BARDA officials and a policy research organization, in the initial years after implementation of the Animal Rule in 2002, the agencies did not always provide aligned feedback to developers. They attributed this in part to the previously noted early lack of clarity regarding FDA's expectations for product approval. However, FDA, BARDA, DOD, and NIH officials; developers; clinical research organizations; and academic research and policy organizations cited steps that the agencies took to improve their information sharing efforts and processes for supporting developers, including the following:[26]

Sharing FDA feedback with BARDA. To help ensure FDA and BARDA have a consistent shared understanding of developers' issues, BARDA officials said that the agency's contracts with developers were updated in 2010 to include provisions that require developers to share all of the developers' communications with FDA with BARDA officials. Previously, developers were not required to update BARDA officials on FDA's feedback, and FDA officials told us developers did not always fully or accurately relay FDA's feedback to BARDA officials. However, BARDA officials said that, beginning in 2010, their contracts have specified that developers are required to provide BARDA with information about scheduled meetings with FDA and minutes from formal and informal meetings with FDA. BARDA is also able to review all developer materials before submission to FDA under the updated contracts. Several developers told us they found BARDA's feedback on their FDA submission materials relevant and helpful in preparing for interactions with FDA. For example, one developer noted that BARDA officials helped prepare submission data according to FDA preferences. FDA officials said that they encourage

[25]FDA can share certain information with BARDA under the ASPR-FDA Memorandum of Understanding. See Food and Drug Administration, *Memorandum of Understanding Between Food and Drug Administration and Office of the Assistant Secretary for Preparedness and Response* (Apr. 16, 2019), accessed June 6, 2022, https://www.fda.gov/about-fda/domestic-mous/mou-225-19-013.

[26]We determined that FDA and BARDA information sharing practices were generally consistent with the information and communication component of federal internal control standards. See GAO-14-704G.

product sponsors to practice full transparency with relevant federal agencies.

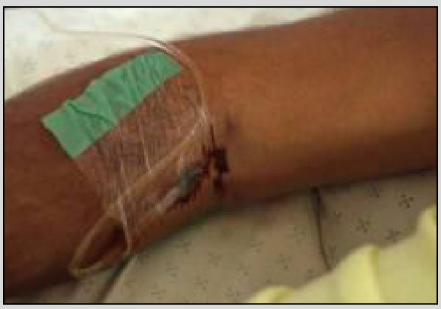
- **BARDA attendance at meetings between medical countermeasure developers and FDA.** A couple of developers noted that having BARDA officials attend developer meetings with FDA has helped ensure that BARDA officials receive information on FDA's feedback and that all parties hear FDA's expectations. For example, one developer told us BARDA officials attended meetings the developer had with FDA to listen to the discussions and remain aware of any updates. One academic research and policy organization said that BARDA is generally involved with meetings between developers and FDA to help ensure developers receive consistent feedback from both agencies.
- **BARDA participation in FDA advisory committee meetings.** Developers, contract research organizations, and an academic research and policy organization noted that FDA advisory committee meetings have helped establish a better shared understanding of relevant research and issues, and have helped identify the appropriate animal models for animal efficacy studies. BARDA officials attended and have presented at several advisory committee meetings held by FDA. For example, in 2011 and 2013 respectively, subject matter experts from BARDA presented at FDA advisory committee meetings about the development of medical countermeasures to treat smallpox and the approval of Botulism Antitoxin Heptavalent, a medical countermeasure for the treatment of botulism.
- **Interagency working groups**. FDA, DOD, and NIH officials cited interagency meetings and working groups as helping with efforts to share and disseminate information about animal models and medical countermeasure development. For example, DOD and NIH agency officials told us that an interagency working group focused on medical countermeasure development for filoviruses, such as Ebola virus disease, has served as a helpful forum for sharing information about filovirus animal models.[27] (See sidebar for information about Ebola virus disease.)
- **Hosting interagency medical countermeasure development workshops.** A few developers, a contract research organization, and an academic research organization cited public interagency workshops hosted by FDA, BARDA, and NIH focused on various

Ebola Virus

Ebola virus disease is highly lethal and can cause illness and death in humans from severe hemorrhagic fever. Case fatality rates average 50 percent and can reach 90 percent. People can contract Ebola virus disease through direct contact with wild animals, a sick or dead person infected with the Ebola virus, or through contact with contaminated surfaces and materials.

From 2014 through 2016, there was an Ebola virus disease outbreak in West Africa. Eleven people, mostly medical workers who became ill in West Africa, were treated for the disease in the U.S. Another outbreak occurred in the Democratic Republic of the Congo from 2018 through 2020.

The Food and Drug Administration (FDA) has approved two treatments and a vaccine for Ebola. Early product studies were conducted under FDA's Animal Rule, which allows the agency to approve products based on evidence from animal efficacy studies when it would be unethical or infeasible to conduct human clinical trials. However, the outbreaks in West Africa and the Democratic Republic of the Congo allowed for human clinical trials to demonstrate the effectiveness of the Ebola products.



A view of a bleeding intravenous site of a patient infected with Ebola virus.

Source: FDA (information), Centers for Disease Control and Prevention (information, photo), World Health Organization (information). | GAO-22-105248

[27]Filoviruses, including the Ebola and Marburg viruses, can cause illness and death in humans from severe hemorrhagic fever.

CBRN agents as helpful in obtaining perspectives from subject matter experts involved in medical countermeasure development and for sharing information about the logistical challenges with animal model research. For example, FDA and BARDA officials participated in a 2017 NIH workshop on the ability to repurpose existing products as medical countermeasures for conditions stemming from acute radiation exposure. One contract research organization said that workshops helped further the development of medical countermeasures for anthrax.[28] (See sidebar for information about anthrax.) One developer also noted that the ability to hold informal discussions with FDA officials during interagency workshops helped clarify the agency's guidance and regulatory expectations.

FDA Has Qualified One Animal Model, but FDA Officials and Stakeholders Said Medical Countermeasure Development Has Not Been Impeded by Lack of Qualified Models

FDA Has Qualified One Animal Model Since 2011

Our review of FDA documentation shows that, since FDA's establishment of the Animal Model Qualification Program in 2011, the agency has qualified one animal model. According to FDA, DOD, and NIH officials and several developers, a variety of reasons have contributed to the limited number of qualified models, including the investment of time and resources needed to submit the necessary information for qualification. According to FDA officials, since the program's inception in 2011, the agency had accepted 11 animal model submissions, with the majority submitted between 2011 and 2014. FDA officials told us the majority of

[28]For example, FDA and BARDA hosted a workshop in November 2007, and FDA presented at a workshop in July 2011 on the development of medical countermeasures for anthrax.

these were submitted by federal agencies involved in animal model development, including NIH, BARDA, and DOD, and two were submitted by academic researchers. FDA had qualified one of the 11 submissions as of April 2022—a cynomolgus macaque model for pneumonic tularemia developed by NIH that FDA qualified in October 2021.[29] (See sidebar for information about tularemia.)

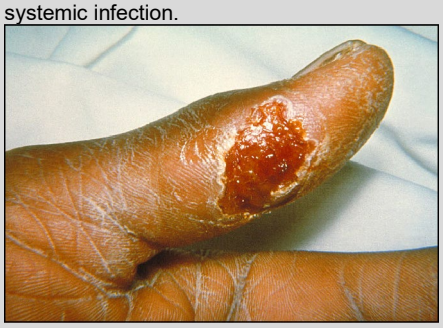
FDA officials told us they had not qualified the other 10 submissions for various reasons. One submission is currently under review by FDA for qualification, while the other nine had not progressed to the qualification stage. FDA officials told us that several submissions included only basic descriptions of the animal models and lacked additional supporting information, such as proposed animal model data collection and analysis plans.

According to officials from FDA and other federal agencies—such as NIH, BARDA, and DOD—that develop animal models and many developers we interviewed, there are several reasons why there are not more qualified models under the Animal Model Qualification Program. FDA officials stated the agency's qualification determination process under the program is rigorous. Developers and federal agencies that develop animal models need to submit sufficient animal modeling data, among other evidence, to meet FDA's qualification standards. FDA bases its qualification on determining both that the animal model reflects key elements of the human experiences with the relevant disease or condition associated with the CBRN exposure, and that it can be appropriately used in animal efficacy studies to develop medical countermeasure products.[30] Officials from federal agencies that have submitted animal models for qualification noted this rigor and the resources required to pursue qualification. NIH officials told us that pursuing qualification of an animal model is resource-intensive because it involves conducting well-controlled and well-documented studies and providing FDA with extensive data and analyses. DOD officials reported that FDA requires a stringent level of evaluation to qualify a model, including requiring a wide range of animal modeling data. For example, DOD officials told us they considered pursuing FDA qualification of an Ebola animal model but determined not

Tularemia

The Food and Drug Administration has qualified an animal model under the Animal Model Qualification Program to help develop products for tularemia. Tularemia is an infectious disease caused by the bacteria Francisella tularensis. Found widely in nature in animals, it could be isolated and used for bioterrorism, likely by being made airborne for exposure by inhalation.

People who inhale dust or aerosols contaminated with Francisella. tularensis bacteria could experience sudden fever, chills, headaches, muscle aches, joint pain, and progressive weakness and, if left untreated, may experience severe respiratory illness, including life-threatening pneumonia and systemic infection.



A close view of a patient's left thumb from the lateral perspective, revealing an ulcerative skin lesion, which was diagnosed as tularemia.

Source: Centers for Disease Control and Prevention (data, photo). | GAO-22-105248

[29]In October 2021, FDA qualified a cynomolgus macaque model of pneumonic tularemia submitted by NIH's National Institute of Allergy and Infectious Diseases. According to NIH officials, NIH has submitted three additional models to FDA's Animal Model Qualification Program that are in various stages of the qualification process.

[30]FDA, *Product Development under the Animal Rule Guidance for Industry.*

to expend the likely resources needed to meet the program's rigorous requirements.

FDA, BARDA, and DOD officials and many developers told us the resource investment required to pursue qualification under the Animal Model Qualification Program may deter developers and federal agencies from pursuing model qualification. For example, they noted that, even when animal models are used to support product approval under the Animal Rule, there is little financial or other incentive for medical countermeasure developers to pursue qualification of the models, because they would need to voluntarily expend additional time and resources to do so. One developer told us it did not have any incentives to pursue qualification once the FDA had approved its product, since obtaining qualification under the Animal Model Qualification Program was so resource-intensive. BARDA and DOD officials and some developers also noted developers' and agencies' competing priorities and resource constraints as reasons not to pursue qualification. For example, DOD officials noted that a developer's priority was to focus on product development and achieve product approval from FDA, rather than to spend time and money obtaining a qualification under the program.

According to Stakeholders, Medical Countermeasure Development Has Not Been Impeded by Lack of Qualified Models

BARDA, NIH, and DOD officials, many developers, and contract research organizations told us the limited number of animal models qualified through FDA's Animal Model Qualification Program has not impeded their product development work. FDA's approval of medical countermeasures under the Animal Rule does not require the use of a qualified model, and developers have used existing animal models to perform animal efficacy studies for their products. Many developers reported obtaining subject matter expertise on which animal models to use from FDA and contract research organizations. In particular, FDA officials and many developers said they met iteratively prior to conducting animal efficacy studies to discuss and determine the appropriate animal models to use.

BARDA, NIH, and DOD officials, some developers, and contract research organizations also reported sharing information about animal models with the close-knit scientific community working on animal models and medical countermeasure product development for their collective benefit. This is done, for example, when developers publish articles on their animal efficacy studies.[31] These articles include information about the specific

[31]These articles may be written in collaboration with contract research organizations that conduct animal studies.

protocols and combinations of animal species used, the method of exposure and dose of the CBRN agent, and the resulting efficacy study data.

Although the use of qualified animal models to develop medical countermeasures has thus far been limited, FDA officials, NIH and DOD officials, some developers, and contract research organizations told us the Animal Model Qualification Program can still provide benefits to future medical countermeasure development. Despite the rigor associated with pursuing animal model qualification, they said having additional animal models qualified could be beneficial to future medical countermeasure development. In particular, they envision that qualified animal models could help reduce medical countermeasure product development time, as having existing animal models to access could limit the time developers spend designing animal models and animal efficacy studies. Having additional animal models qualified could also help clarify FDA expectations early in the product development process. For example, DOD officials told us they found the qualified animal model for tularemia provided efficiencies for their product development work.

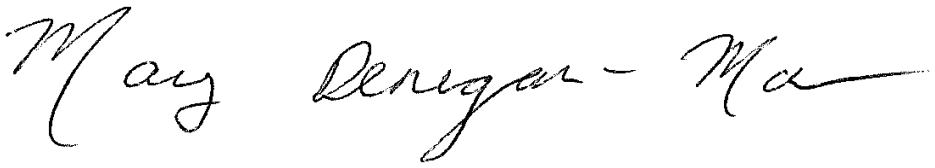
FDA officials told us that publicly disseminating detailed information about qualified animal models will make the models easier to replicate in other studies. They also said having qualified animal models for high-priority CBRN threats without approved medical countermeasures could help encourage future product development for those threats. Further, there may be little risk in maintaining the program, as FDA officials told us that the program requires limited agency resources to administer and does not have dedicated staff.

Agency Comments

We provided a draft of this report to HHS and DOD. HHS and DOD provided technical comments, which we incorporated as appropriate.

We are sending copies of this report to the Secretary of Health and Human Services, the Secretary of Defense, appropriate congressional committees, and other interested parties. In addition, the report is available at no charge on the GAO website at https://www.gao.gov.

If you or your staffs have any questions about this report, please contact me at (202) 512-7114 or DeniganMacauleyM@gao.gov. Contact points for our Offices of Congressional Relations and Public Affairs may be found on the last page of this report.



Mary Denigan-Macauley
Director, Health Care

Appendix I: Interview Selection Methodology

To review the development of medical countermeasures under the Food and Drug Administration's (FDA) Animal Rule, we interviewed officials from federal agencies that support the development of medical countermeasures under the Animal Rule. These includes FDA and the Department of Defense (DOD). We also interviewed officials from the Office of the Assistant Secretary for Preparedness and Response's Biomedical Advanced Research and Development Authority (BARDA), and obtained written responses from the National Institutes of Health (NIH).

We also interviewed representatives from six of the 10 medical countermeasure developers (developers) that have received approval for products under FDA's Animal Rule since 2012.[1] We interviewed Amgen, Chimerix, Elusys Therapeutics, Emergent Biosolutions, and SIGA Technologies. We obtained written responses from Janssen. Five of the six developers we interviewed had approved products that were supported by BARDA. For the four developers we were unable to interview, two declined to speak with us citing issues identifying staff with relevant institutional knowledge, and two were acquired by other companies.[2]

We interviewed the three contract research organizations that conducted animal studies for approved Animal Rule products. We selected these three contract research organizations for interviews based on a contractual relationship with BARDA to develop animal models for Animal Rule product development and for having conducted animal efficacy studies for approved Animal Rule products. We interviewed representatives from Battelle, Lovelace Biomedical, and Southern Research.

We interviewed four academic research and policy organizations with knowledge of medical countermeasure development under the Animal

[1]We focused our interviews on developers that developed medical countermeasures after implementation of the Animal Rule. Two medical countermeasures, pyridostigmine bromide and Cyanokit, were approved under the Animal Rule prior to 2012 but had been developed before the Animal Rule's implementation. Pyridostigmine bromide was used during the Persian Gulf War in 1990 and 1991 as a pretreatment for nerve agents, and the active pharmaceutical ingredient in Cyanokit received marketing approval in France in 1996 for cyanide exposure.

[2]Human Genome Sciences, Inc., developer of Raxibacumab, was acquired by another pharmaceutical company in 2012, and Emergent Biosolutions later acquired the rights to the product in 2017. Cangene, developer of BAT and Anthrasil, was acquired by Emergent Biosolutions in 2014.

Rule. We selected the four academic research and policy organizations based on Internet searches on the Animal Rule, a review of journal and academic articles on medical countermeasure development under the Animal Rule, and a snowball approach of asking interviewees about relevant organizations. We interviewed representatives from the Biotechnology Innovation Organization, Bipartisan Commission on Biodefense, Johns Hopkins Center for Health Security, and University of Maryland School of Medicine Medical Countermeasure Program.

Appendix II: GAO Contact and Staff Acknowledgments

GAO Contact

Mary Denigan-Macauley, (202) 512-7114 or DeniganMacauleyM@gao.gov

Staff Acknowledgment

In addition to the individual named above, Kelly DeMots (Assistant Director), Michael Erhardt (Analyst-in-Charge), Christina Lee, and Marie Suding made key contributions to this report. Also contributing were Kaitlin Farquharson, Diona Martyn, Laurie Pachter, and Ethiene Salgado-Rodriguez.