

GAO

Report to the Ranking Member,
Committee on Energy and Commerce,
House of Representatives

October 2010

FOOD AND DRUG ADMINISTRATION

Response to Heparin
Contamination Helped
Protect Public Health;
Controls That Were
Needed for Working
With External Entities
Were Recently Added



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Highlights of [GAO-11-95](#), a report to the Ranking Member, Committee on Energy and Commerce, House of Representatives

Why GAO Did This Study

In early 2008, the Food and Drug Administration (FDA) responded to a crisis involving the contamination of heparin, a medication used to prevent and treat blood clots, when the agency received multiple reports of adverse events involving severe allergic reactions. The crisis took place from January 2008 through May 2008, during which time FDA took several actions in its response to the crisis.

GAO was asked to review FDA's management of the heparin crisis. This report examines (1) how FDA prevented additional contaminated heparin from reaching U.S. consumers, (2) how FDA coordinated its response to the contaminated heparin crisis, and (3) FDA's monitoring and analysis of adverse events associated with heparin.

To conduct this review, GAO reviewed relevant FDA documents, regulations, and guidance; analyzed FDA data; and interviewed FDA officials and other experts involved in the crisis and knowledgeable about drug quality standards.

View [GAO-11-95](#) or key components. For more information, contact Marcia Crosse at (202) 512-7114 or crossem@gao.gov

October 2010

FOOD AND DRUG ADMINISTRATION

Response to Heparin Contamination Helped Protect Public Health; Controls That Were Needed for Working With External Entities Were Recently Added

What GAO Found

In its response to the heparin crisis, FDA took several actions related to its responsibility to protect the public health by ensuring the safety and security of the nation's drug and medical device supplies. FDA increased its activities related to oversight of heparin firms by conducting inspections and investigations and monitoring heparin imports, and worked with drug and device manufacturers to recall contaminated products while ensuring that an adequate supply of uncontaminated heparin was available. With the help of external entities, FDA identified the unknown contaminant and developed tests to screen all heparin products. Additionally, the agency reached out to its international regulatory partners during the crisis. However, FDA faced some limitations in its efforts to inspect heparin firms in China and collaborate internationally, and the agency was unable to determine the original source of contamination.

FDA coordinated internal and external resources to respond to the contaminated heparin crisis, but did not address risks related to working with certain external entities with ties to heparin firms. The agency has issued standards of ethics regarding collaboration with external entities and governmentwide standards apply to the acceptance of services provided free of charge. Despite these existing standards, FDA did not have processes in place to ensure that it considered or applied them when it accepted assistance from external entities with ties to heparin firms on a voluntary basis during the heparin crisis. Not adequately addressing these risks could have affected the public's confidence in FDA's response efforts and in its other activities related to the regulation of heparin products and also left FDA open to claims for payment for services that these external entities provided to FDA.

FDA monitored trends in the number of reports of adverse events associated with heparin drug products and heparin-containing medical devices that it received before, during, and after the crisis. FDA also conducted analyses of adverse events, including deaths, associated with heparin drug products and heparin-containing medical devices. However, FDA was unable to determine if any of the adverse events or deaths were linked to contaminated heparin because of data limitations and confounding factors regarding the individual patients, such as the natural course of the underlying disease or condition.

In the draft report we provided to the Department of Health and Human Services for comment, we recommended that FDA develop adequate controls to help avoid exposure to risks when working with external entities in future situations similar to the heparin crisis. In response, FDA issued guidance on October 15, 2010, for FDA staff to follow when working with external scientific and other experts in emergency situations when the services are provided on a gratuitous basis. FDA also stressed the unprecedented nature of the heparin crisis and noted various actions it took in response to the crisis.

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Abbreviations

AEG	Agency Executive Group
AERS	Adverse Event Reporting System
AIC	Agency Incident Coordinator
API	active pharmaceutical ingredient
APP	APP Pharmaceuticals
CDC	Centers for Disease Control and Prevention
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
EOP	<i>Emergency Operations Plan</i>
ERP	<i>Emergency Response Plan</i>
FDA	Food and Drug Administration
GMP	good manufacturing practice
HHS	U.S. Department of Health and Human Services
LMWH	low molecular weight heparin
MAUDE	Manufacturer and User Facility Device Experience
MOA	memorandum of agreement
MPS	China's Ministry of Public Security
NAI	no action indicated
OAI	official action indicated
OCM	Office of Crisis Management
ORA	Office of Regulatory Affairs
OSCS	over-sulfated chondroitin sulfate
PT	preferred term
SFDA	State Food and Drug Administration of the People's Republic of China
SMQ	Standardized MedDRA Query
SMQ+	Standardized MedDRA Query Plus
UFH	unfractionated heparin
USP	United States Pharmacopeia
VAI	voluntary action indicated

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United States Government Accountability Office
Washington, DC 20548

October 29, 2010

The Honorable Joe Barton
Ranking Member
Committee on Energy and Commerce
House of Representatives

Dear Mr. Barton:

In 2008, the Food and Drug Administration (FDA) responded to a crisis involving the contamination of heparin, a medication that is used to prevent and treat blood clots.¹ Beginning in early January of that year, FDA and the Centers for Disease Control and Prevention (CDC) received multiple reports of adverse events involving severe allergic reactions in dialysis patients. While the cause of these events was initially unknown, about 2 days after CDC received the reports of adverse events, CDC determined that these reactions were possibly associated with heparin manufactured by Baxter Healthcare Corporation (Baxter) and notified FDA of the association.² CDC and FDA confirmed that Baxter heparin was involved about 3 weeks later, after both agencies gathered more information about the reactions. By late January, FDA determined that the active pharmaceutical ingredient (API) used to manufacture the contaminated Baxter heparin came from a facility in China.³

¹The drug heparin is typically administered to patients intravenously. However, patients may also receive heparin through the use of medical devices that contain or are coated with heparin, such as catheters, vascular stents, and tubing.

²Following this preliminary work, CDC conducted an epidemiological review of 152 adverse events associated with heparin in patients in dialysis centers from November 19, 2007, through January 31, 2008. D. B. Blossom, et al., "Outbreak of Adverse Reactions Associated with Contaminated Heparin," *New England Journal of Medicine*, vol. 359, no. 25 (2008).

³An active pharmaceutical ingredient is any substance or mixture of substances intended to be used in the manufacture of a drug (medicinal) product and that, when used in the production of a drug, becomes an active ingredient of the drug product. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure and function of the body.

Heparin is a medically necessary drug that is used by millions of patients in the United States each year.⁴ It is commonly used before certain types of surgery, including coronary artery bypass graft surgery; in kidney patients before they undergo dialysis; and to prevent or treat other serious conditions, such as deep vein thrombosis and pulmonary emboli. Heparin is also used in medical devices—for example, some blood oxygenators and catheters contain or are coated with heparin, and some diagnostic testing products such as capillary tubes are manufactured using heparin.

In January and February 2008, FDA worked to facilitate recalls of contaminated heparin and heparin-containing devices once the agency determined that a recall would not create a heparin shortage. In early February, FDA engaged external scientists to assist the agency in identifying the unknown contaminant and in developing tests to detect this contaminant. In late February, FDA formed an internal task force to manage its response to the crisis and engaged additional external scientists when more heparin expertise was needed to identify the specific contaminant in heparin. The tests to detect whether or not heparin contained a contaminant were made public in early March, and FDA identified the specific contaminant in mid-March. In April 2008, FDA held an international conference with regulators and other stakeholders throughout the world to discuss the heparin problem, its solution, and how to prevent similar future crises. Throughout the crisis, FDA held media briefings and monitored heparin-associated adverse events. FDA determined the crisis was over by the end of May 2008, and its internal task force discontinued regular meetings.

FDA officials believe that the contamination of heparin was an instance of economically motivated adulteration.⁵ Several instances of adulterated products have occurred in the past, including infant formula, pet food, and toothpaste, and FDA has stated that future instances of adulteration remain a public health threat. Therefore, it is likely that the agency will

⁴FDA considers a product to be medically necessary, or a medical necessity, if it is used to treat or prevent a serious disease or medical condition, and there is no other available source of that product or alternative drug or therapy that is judged by medical staff to be an adequate substitute. According to FDA, patient “inconvenience” alone is an insufficient basis to classify a product as a medical necessity.

⁵FDA’s working definition of “economically motivated adulteration” is the fraudulent, intentional substitution or addition of a substance in a product for the purpose of increasing the apparent value of the product or reducing the cost of its production, i.e., for economic gain. 74 Fed. Reg. 15497 (Apr. 6, 2009).

have to respond to similar large-scale public health crises involving FDA-regulated products in the future.

Responding to public health crises is a part of FDA's mission to protect the public health, which includes ensuring the safety and efficacy of the nation's drug and medical device supplies. As part of its efforts to ensure the safety and efficacy of drugs and medical devices, FDA conducts oversight activities, collaborates with external entities, and communicates information to the public. FDA has recognized that to preserve the public trust, its actions should adhere to certain principles of integrity, and it has developed guidance to help ensure that the agency does not compromise the integrity or the appearance of integrity of its programs or the officials who manage them. In addition, FDA is to carry out its responsibilities in a manner consistent with other applicable laws and guidance, including those related to the use of public funds.

You asked us to review FDA's management of the contaminated heparin crisis. In this report, we examine (1) how FDA prevented additional contaminated heparin from reaching U.S. consumers, (2) how FDA coordinated its response to the contaminated heparin crisis, and (3) FDA's monitoring and analysis of adverse events associated with heparin.

To examine how FDA prevented additional contaminated heparin from reaching U.S. consumers, we reviewed actions FDA took during the crisis period, which FDA defined as January 2008 through May 2008. We also interviewed FDA officials and drug manufacturers and reviewed FDA documents including inspection reports, investigation memorandums, warning and untitled letters, testing records, meeting minutes, records of correspondence, conference documents, media briefing transcripts, public communications, database reports, and internally produced summaries (such as a timeline of events related to the crisis). Additionally, we reviewed laws, regulations, and guidance relevant to FDA's authorities regarding inspections and investigations, imports, enforcement, recalls, and drug shortages. In addition, we examined documents related to FDA's international cooperation with foreign regulatory agencies. We conducted analyses of FDA data on heparin-related inspections and investigations, testing of imported heparin, and heparin product recalls. We also reviewed other relevant documents, such as congressional testimonies and our previous reports. In addition, we used our interviews and document reviews to learn about any FDA efforts and initiatives that might help avoid similar crises in the future.

To examine how FDA coordinated its response to the contaminated heparin crisis, we interviewed FDA and CDC officials, drug manufacturers, consumer advocacy groups, and academic researchers involved in or knowledgeable about the contaminated heparin crisis, as well as officials from the United States Pharmacopeia (USP), the entity that sets drug quality standards in the United States. We examined FDA's ability to work with external entities and related guidance to learn how FDA works with external entities that have a formal relationship with FDA, as well as federal statutes and administrative materials on the acceptance of uncompensated services.⁶ We also reviewed relevant FDA documents, including meeting minutes, records of correspondence, conference documents, and internally produced summaries. Additionally, we reviewed FDA's *Emergency Response Plan* (ERP) to examine the agency's framework for responding to emergencies, and reviewed FDA's draft guidance for responding to future emergencies.

To examine FDA's monitoring and analysis of adverse events associated with heparin, including deaths, we interviewed FDA officials and reviewed relevant documents, including two FDA analyses of adverse event reports associated with heparin drug products, and we also reviewed an FDA analysis of adverse events associated with heparin-containing medical devices. To assess trends in heparin-associated adverse events that occurred before, during, and after the crisis, we also reviewed FDA data on heparin-associated adverse event reports—from January 2007 through September 2009 for reports associated with heparin drug products, and from January 2005 through September 2009 for reports associated with heparin-containing medical devices. In addition, to understand the limitations of the data FDA analyzed, we reviewed the 94 death reports associated with heparin drug products that FDA included in its analyses of heparin adverse event reports.

To assess the reliability of the FDA data we used under each objective, we took several steps that included determining how FDA entered information into its databases, reviewing FDA's validation processes for its databases, discussing any limitations, and corroborating data with information from other sources where possible. We determined that all of the data we reviewed were sufficiently reliable for the purposes of this

⁶We use the term "external entities" to refer to nongovernmental organizations and experts who offer expertise to the agency but who are not permanent employees of the agency. For example research institutes, drug firms, and individual scientists from universities could be considered external entities.

report. We conducted this performance audit from June 2009 through September 2010 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

FDA conducts a variety of activities pursuant to its mission to protect the public health. To carry out these functions, FDA is organized into product centers—which regulate products including human and veterinary drugs, vaccines and other biological products, medical devices, most food, and tobacco—a research center, which provides scientific technology, training, and technical expertise, and offices that carry out various functions of the agency. FDA’s response to the contaminated heparin crisis involved a number of FDA centers and offices.

FDA

FDA’s activities related to its mission and relevant to the heparin crisis include the following:

- **Overseeing drug and device firms.**⁷ FDA conducts oversight activities such as inspections and investigations of foreign and domestic manufacturing firms, including their suppliers, to determine compliance with good manufacturing practices (GMP), or sampling of imported products. FDA also takes regulatory actions against firms, when appropriate, by issuing warning letters, detaining imports, or recommending seizure of products.⁸

⁷We use the term “firm” to refer to entities that are involved in manufacturing, testing, or shipping of products. Drug and device firms may be comprised of more than one establishment; that is, establishments under the same firm may include, for example, manufacturing facilities and storage warehouses.

⁸An inspection is an examination of a manufacturing facility to determine compliance with applicable law and FDA regulations, and an Establishment Inspection Report is written to document it. An investigation is information gathering conducted with the purpose of determining and documenting facts concerning a particular issue, such as a disaster, product tampering, or complaint follow-up. A memorandum is almost always prepared based on the information gathered in an investigation. FDA regulations on good manufacturing practices require manufacturers to meet certain specifications in the manufacturing process to ensure that their products are safe and have the identity, strength, quality, and purity that their products purport to have. GMP requirements apply to finished drug products and active pharmaceutical ingredients, as well as devices. *See* 21 U.S.C. § 351(a)(2)(B), 21 C.F.R. pts. 210, 211, 820 (2010).

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- **Collaborating with USP.**⁹ FDA collaborates with USP to help ensure the safety and quality of drug products. Under the Federal Food, Drug, and Cosmetic Act, prescription and over-the-counter drugs sold in the United States generally must comply with quality standards published in the *USP-National Formulary*.¹⁰ USP sets standards for drug quality, purity, and strength, as well as the tests or methods used to assess quality, purity, and strength. Products that do not meet USP standards using the specified methods are considered adulterated by law.
 - **Collaborating with foreign regulatory agencies.** FDA has confidentiality commitments to facilitate information sharing with regulatory agencies in 19 countries, including Australia, Canada, France, Germany, and Japan.¹¹ FDA does not have a confidentiality commitment with China; however, FDA negotiated two memorandums of agreement with China in 2007 aimed at improving the safety of Chinese drug products and medical devices, and food exported to the United States.¹² In recent years, FDA has opened offices abroad, including in India, Europe, Latin America, and China. FDA opened its office in China in November 2008, with posts in Beijing, Shanghai, and Guangzhou. An FDA official said the primary mission of these offices is to help gather more information on the safety and quality of products that are being exported to the United States so that FDA can make better-informed decisions about which products to permit to enter the United States.
 - **Monitoring adverse events.** FDA monitors drug and device safety through its postmarketing surveillance program. FDA's Adverse Event Reporting System (AERS) is a database that supports the agency's postmarketing safety surveillance program for all approved drug and therapeutic biologic products. FDA uses AERS to record adverse event reports and to monitor for new adverse events and medication errors associated with drug products marketed in the United States. FDA uses its

⁹USP is a nongovernmental, public standards-setting authority for prescription and over-the-counter drugs that are manufactured or sold in the United States.

¹⁰See 21 U.S.C. §§ 321(j), 351(b).

¹¹FDA also has commitments with the European Commission and the World Health Organization. A list of entities with confidentiality commitments with FDA and links to the commitments can be found at <http://www.fda.gov/InternationalPrograms/Agreements/ConfidentialityCommitments/default.htm> (accessed July 8, 2010).

¹²A copy of FDA's agreement with China regarding drugs and medical devices can be found at <http://www.fda.gov/InternationalPrograms/Agreements/MemorandaofUnderstanding/ucm107512.htm> (accessed July 12, 2010).

Manufacturer and User Facility Device Experience (MAUDE) database to record and monitor reports of adverse events related to medical devices.¹³

- **Communicating with the public.** FDA communicates information to the public through a variety of means, including press releases, media briefings, public health advisories, and news interviews. FDA also disseminates information on the agency's Web site, including regulatory information, scientific research, and educational materials.
- **Responding to emergencies.** To respond to emergencies or crises, FDA uses a plan to assist the agency in organizing a coordinated response to events involving FDA-regulated products as well as other identified public health emergencies. At the time of the heparin crisis, FDA had its ERP in place, which was issued in February 2005.
- **Working with external entities.** When necessary, FDA enters into working relationships with external entities, such as scientists from universities or drug firms, to assist the agency with matters such as the review of research and product applications. For example, scientists serving on advisory committees review and make recommendations on drug applications, and scientists from universities provide expertise in specific scientific disciplines and enhance the science base of the agency through FDA's Science Advisor Program. FDA has guidance in place for working with external entities in certain situations, including a guide called *The Leveraging Handbook*.¹⁴ This handbook references statutes and regulations that apply to the behavior of individual FDA employees. It also contains guidance applicable to FDA as an agency to prevent public perception concerns and demonstrate that the agency is worthy of public trust in carrying out its activities. In addition, other laws, regulations, and policies may apply to FDA's work with external entities, depending on the nature of the arrangements. FDA, like other federal agencies, generally may not accept voluntary services, which may give rise to claims for

¹³Generally, if a manufacturer receives drug- or certain device-related adverse event reports, it must send them to FDA. Health care professionals and consumers can voluntarily file adverse event reports with FDA and may also report these events to the products' manufacturers. User facilities (e.g., hospitals and nursing homes) must report certain device-related—but not drug-related—adverse events to FDA as well. 21 C.F.R. §§ 314.80(c), 803.30, 803.50 (2010).

¹⁴See U.S. Department of Health and Human Services, Food and Drug Administration, *The Leveraging Handbook—An Agency Resource for Effective Collaborations, Final Guidance*, February 2003, Corrected June 2003 (Rockville, Md., 2003), <http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/WhatWeDo/UCM121662.pdf> (accessed July 28, 2010).

payment for which funds are not available. However, with a written agreement that services are provided with no expectation of payment, FDA may accept uncompensated services from external entities.

Heparin and the Contaminated Heparin Crisis

Heparin is a medically necessary drug that acts as an anticoagulant; that is, it prevents the formation of blood clots in the veins, arteries, and lungs (see app. I for technical information on heparin and research related to contaminated heparin). The heparin supply chain starts with a raw source material, primarily derived from the intestines of pigs, that is processed into crude heparin. China is the primary source of crude heparin for U.S. manufacturers because of its abundant pig supply. Thousands of small pig farms in Chinese villages extract and process pig intestines in small workshops called casing facilities. Consolidators collect different batches of heparin, typically called heparin lots, from various workshops and combine them into single heparin lots. The consolidators sell the crude heparin lots to manufacturers, who further refine the crude heparin into heparin API, the active ingredient used in heparin drug products and devices. More than half of the finished heparin products in the United States and globally are made from Chinese-sourced materials.

There are seven pharmaceutical companies that manufacture and distribute heparin products in the United States. At the time of the crisis, Baxter and APP Pharmaceuticals (APP) were the two largest manufacturers of heparin in the United States, with each company accounting for about half of the total U.S. heparin supply. Both companies received the majority of their crude heparin from Chinese sources.

Several FDA centers and offices were involved in the response to the contaminated heparin crisis. Some of these centers and offices and their relevant functions are described below (see app. II for a complete list of FDA centers, offices, and divisions that were involved in the heparin crisis):

- **Office of the Commissioner**—leads FDA and implements FDA’s mission.
- **Office of Crisis Management (OCM)**—develops crisis management policies, leads and coordinates the agency’s development and updating of emergency preparedness and response plans, including FDA’s ERP, and coordinates the agency’s emergency response.
- **Office of International Programs**—works with agencies and governments to advance public health worldwide.

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- **Office of Regulatory Affairs (ORA)**—leads inspections of regulated domestic and imported products and domestic and foreign manufacturing facilities, and develops enforcement policies.
 - **Center for Drug Evaluation and Research (CDER)**—regulates over-the-counter and prescription drugs, including biological therapeutics and generic drugs sold in the United States.
 - **Center for Devices and Radiological Health (CDRH)**—regulates medical and radiological devices sold in the United States.

FDA Took Multiple Steps to Protect U.S. Consumers from Additional Contaminated Heparin, but Faced Limitations in Oversight and Collaboration

FDA took several actions during the first half of 2008 to protect the public health in response to the heparin crisis. During that time and afterwards, FDA increased oversight of heparin firms, but sometimes faced limitations in oversight and collaborating with others. FDA also worked with heparin manufacturers to recall contaminated heparin products while ensuring an adequate supply for U.S. consumers. In addition, FDA collaborated with its international regulatory partners to exchange information. Because of limitations related to conducting inspections and investigations of heparin firms in China, FDA could not determine the original source of the heparin contamination.

FDA Took Action through the First Half of 2008 to Protect the Public Health in Response to the Heparin Crisis

To respond to the heparin crisis, FDA took action related to its responsibility to protect the public health by ensuring the safety and security of the nation's drug and medical device supplies by taking various actions from January through May 2008. On January 7, 2008, after FDA learned about the severe allergic reactions taking place, the agency initiated an investigation at the dialysis facility where the first observed allergic reactions took place and shared information with CDC. At the same time, FDA contacted a medical device manufacturer since it was initially thought the allergic reactions were in response to a medical device. After FDA learned that the problem possibly was associated with Baxter heparin, on January 9, 2008, the agency began investigations and inspections of heparin drug and device firms.

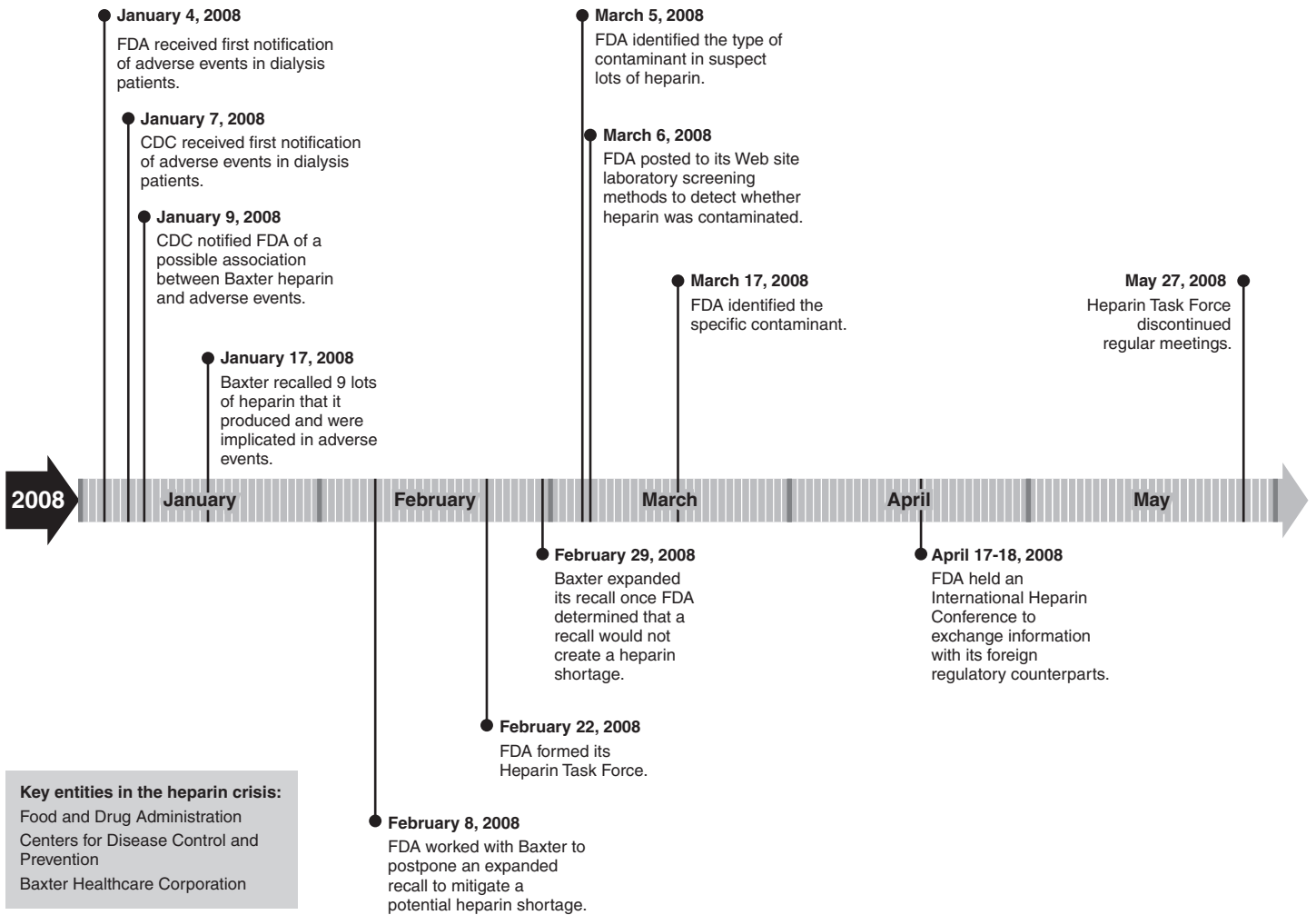
FDA received notification of the first recall of nine lots of Baxter heparin products, which took place on January 17, 2008, and began work with this drug firm to learn more about the problem with its heparin. By January 23, FDA learned that Baxter received its heparin API from

Scientific Protein Laboratories' (SPL) establishments in Wisconsin and China. In early February 2008, the agency worked to postpone an expanded recall of Baxter's heparin products so it could consult with APP to ensure that APP could supply the U.S. heparin market and mitigate a potential heparin shortage. The second recall, which included all lots of Baxter's single and multidose vial heparin products, took place on February 29, 2008. FDA also facilitated recalls of heparin-containing medical devices with heparin device firms.

As the crisis progressed, FDA took additional actions in February and March 2008. By late February, FDA could distinguish contaminated heparin from uncontaminated heparin using preliminary testing methods and continued working to develop these methods. During that month, FDA also formed an internal task force to coordinate the agency's response to the heparin crisis and reached out to external scientists to assist the agency in identifying the unknown contaminant and to develop tests to detect this contaminant. On March 5, 2008, FDA identified the type of contaminant in suspect heparin lots and by March 6, it shared newly developed testing methods that could differentiate contaminated heparin from uncontaminated heparin. Some other countries also found contamination in their heparin supplies. Later that month, on March 17, FDA identified oversulfated chondroitin sulfate (OSCS) as a contaminant in the heparin associated with adverse events in the United States.

Additionally, because the majority of finished heparin products in the United States and globally are made with ingredients from China, FDA worked to ensure the safety of heparin imports. Throughout the crisis, FDA also provided information about the crisis to a variety of audiences, including the press, physicians, and medical facilities. By April 2008, the agency determined that the number of adverse events involving heparin had returned to precrisis levels. FDA held an international heparin conference on April 17, and 18, 2008 to exchange information with its foreign regulatory counterparts. FDA's task force continued to meet until May 27, 2008, when it was determined that the crisis was over. Figure 1 shows the timeline of key events in the heparin crisis.

Figure 1: Timeline of Key Events in the Heparin Crisis



Source: GAO analysis of FDA information.

FDA Increased Its Oversight of Heparin Firms, but Faced Limitations in Its Actions Regarding Some Firms in China

In response to the heparin crisis, FDA increased its oversight activities of heparin firms by increasing its inspections, investigations, and monitoring efforts.

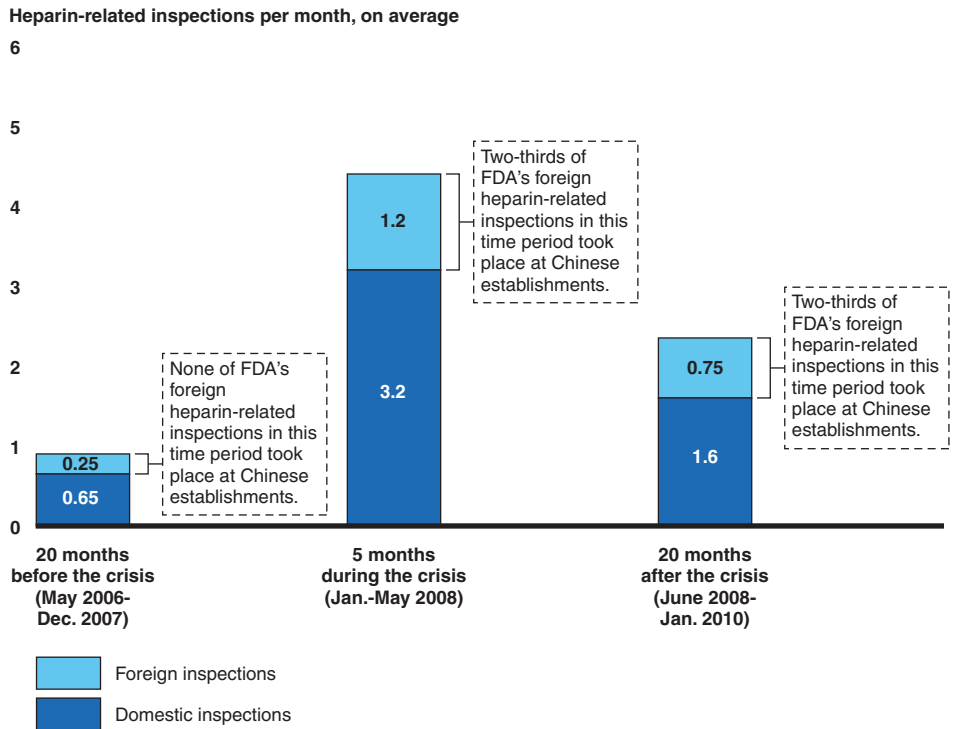
- **Inspections.** During and after the crisis, FDA conducted an increased number of domestic and foreign heparin-related inspections of drug and device firms compared with the number of inspections prior to the crisis (see fig. 2).¹⁵ In particular, FDA increased its frequency of inspections of Chinese firms associated with OSCS contamination in the United States. In the 20-month period prior to the crisis, FDA did not conduct any inspections of Chinese heparin firms. In contrast, 11 Chinese firms constituted 14 of the 21 heparin-related foreign inspections conducted by FDA during and after the crisis.¹⁶ Of the Chinese firms that FDA inspected, only 2 had been inspected prior to the contaminated heparin crisis.¹⁷

¹⁵These numbers of foreign and domestic heparin-related inspections represent all heparin-related inspections of which we are aware and for which we were able to obtain documentation from FDA.

¹⁶In this analysis we defined the 20-month period before the crisis as May 2006–December 2007, the 5-month period during the crisis as January–May 2008, and the 20-month period after the crisis as June 2008–January 2010.

¹⁷FDA officials told us that prior to the contaminated heparin crisis, the agency did not usually inspect crude heparin manufacturers and instead focused on API manufacturing facilities. According to FDA’s heparin-related inspection reports, there were both crude and API Chinese heparin firms that had never been previously inspected. However, the classification was not always clear: In one inspection report, for example, FDA considered a manufacturer of crude heparin to be an API manufacturer, while in another the inspectors described the manufactured material as “crude heparin sodium API.” FDA officials told us that their classification of crude heparin and heparin API depends on various processing steps and the unique circumstances in which the products are used. Officials also told us that some firms have challenged the agency in its attempt to regulate crude heparin.

Figure 2: Average Monthly Domestic and Foreign Heparin-Related Inspections Conducted by FDA before, during, and after the Contaminated Heparin Crisis



Source: GAO analysis of FDA data.

Notes: The inspections in this figure include preapproval inspections, GMP inspections, and inspections that include both preapproval and GMP components. FDA may conduct preapproval inspections of domestic and foreign establishments before approving a new drug or device to be marketed in the United States. The agency conducts GMP inspections to ensure that manufacturers of drugs and devices already marketed in the United States are meeting specifications and producing safe and effective products, in accordance with FDA GMP regulations. See 21 C.F.R. pts. 210, 211, 820 (2010).

Inspections are classified as occurring before, during, or after the crisis based on the month in which they were initiated by FDA.

FDA officials said that there were and continue to be significant legal and practical challenges to conducting inspections of crude heparin manufacturers and the casing facilities that supply them,¹⁸ such as the limits on FDA’s ability to require foreign establishments to allow the agency to inspect their facilities, the large number of and incompleteness

¹⁸Casing facilities are the workshops where the process of extracting and processing pig intestines to make crude heparin takes place.

of FDA's information on the casing facilities, and the expenses associated with conducting foreign inspections. For these reasons, according to FDA officials, FDA focused on firms' responsibilities to ensure that they could trace their crude heparin back to qualified suppliers that produce an uncontaminated product. Furthermore, according to officials, during these inspections FDA inspectors requested that firms conduct their own investigations of any heparin products for which they received complaints or that did not meet specifications.

- **Investigations.** In addition to inspections, FDA conducted investigations at U.S. health care facilities and device firms, domestic drug firms, and a foreign drug firm. FDA data show that the agency conducted at least 37 domestic and 1 foreign investigations related to heparin between January 2008 and June 2009, with individual investigations sometimes consisting of FDA visits to multiple facilities, such as a drug firm and a health care provider. The reasons for these investigations included, for example, obtaining heparin samples, collecting information on firms' crude and heparin API suppliers, following up on patient adverse event reports and the status of product recalls, and witnessing the destruction of contaminated heparin.
- **Monitoring imports.** Beginning in February 2008, FDA began monitoring heparin products offered for import by physically examining and detaining products to help ensure that additional contaminated heparin did not reach U.S. consumers. The agency initially issued an import bulletin in late February 2008 instructing FDA staff to assess the admissibility of heparin products offered for import,¹⁹ and then replaced it with a plan in mid-March 2008 to physically sample and test these products for OSCS contamination. This testing plan, which provided more detailed instructions than the import bulletin, required that FDA test all imported heparin API, and other imported heparin products, on a case-by-case basis, for contamination upon arrival at the U.S. border unless U.S. firms had already committed to testing their imported heparin products using FDA's

¹⁹According to FDA, import bulletins are generally intended for informational purposes only and might not provide policy or coverage guidance. For example, FDA's heparin import bulletin, issued February 27, 2008, instructed FDA's district offices to contact headquarters when imported heparin shipments arrived at the U.S. border, but did not provide more specific instructions for what to do with the heparin shipments.

newly developed testing methods.²⁰ According to FDA data, by the end of June 2010, FDA had collected 141 heparin samples. Three of these samples were contaminated with OSCS, including 1 detected after the crisis period ended in May 2008.²¹

During and after the crisis, FDA also added a total of seven heparin-related establishments associated with OSCS contamination to an existing import alert for drug manufacturers found to be in violation of GMPs, which enabled the agency to detain heparin imports from these establishments without physically examining them.²² FDA officials said that these heparin establishments appeared to stop shipping heparin to the United States after being added to this import alert.

In some instances, FDA took further action as a result of its inspections and import testing. Between April 2008 and April 2009, the agency issued three warning letters and two untitled letters related to the heparin crisis to drug firms.²³ The agency also added the seven heparin establishments to the import alert described previously as a direct result of various factors,

²⁰FDA initially had to request this commitment from manufacturers because the agency's newly developed testing methods were not validated and incorporated into USP's heparin monograph. FDA worked with USP to update its heparin monograph with these methods, which were officially incorporated on June 18, 2008, and during this time FDA requested monthly testing results from firms that had committed to testing. Beginning in March 2009, the monthly updates on heparin test results were no longer required; however, FDA requested that firms notify the agency of any positive results within 3 days of the testing. FDA and USP officials told us that they worked together on a second revision, which included a more precise testing method and was issued in October 2009. In addition, a USP official told us that both agencies are currently working together on a third revision of the heparin monograph that will focus in part on further increasing test sensitivity and detection of impurities.

²¹FDA collected an OSCS-contaminated sample of crude heparin sodium in December 2008 from a shipment manufactured and shipped by a Chinese firm.

²²FDA added these seven establishments to its existing Import Alert 66-40, "Detention without Physical Examination of Drugs from Firms Which Have Not Met Drug GMPs," which was issued prior to the contaminated heparin crisis to detain products from specific drug establishments that FDA determined through inspections to be in violation of GMPs. Unlike import bulletins, import alerts provide guidance for import coverage. FDA is authorized to detain or refuse products when offered at the U.S. border for import if the products appear to be adulterated "from the examination of such samples or otherwise . . ." 21 U.S.C. § 381(a)(3), (b).

²³FDA issues warning letters to regulated manufacturers to notify them of violations of regulatory significance. In contrast, FDA issues untitled letters to manufacturers to notify them of violations that do not meet the threshold of regulatory significance for a warning letter.

including deficiencies observed during inspections, detection of contaminated heparin during import testing, and FDA's determination that establishments were not adequately safeguarding their heparin supply chains. Additionally, FDA initiated a seizure of heparin products from one firm after the agency determined that the firm's efforts to voluntarily recall contaminated heparin products identified during an inspection were inadequate.²⁴

However, FDA officials believed that they had limited authority to take action when they encountered refusals, either by the firm or by the Chinese government, to permit a full inspection of some Chinese firms. In two instances, Chinese crude heparin consolidators refused to provide FDA full access during limited inspections—in particular, one consolidator refused to let FDA inspectors walk through its laboratory and refused FDA access to its records.²⁵ FDA classified both limited inspections as “no action indicated” (NAI) and did not attempt to reinspect the facilities, document any objectionable conditions, or place the firms on import alert.²⁶ FDA officials provided us with various reasons why FDA classified these limited inspections as NAI and did not pursue these firms further despite encountering refusals. FDA officials told us that the agency focused its efforts on the API manufacturers that these firms supplied.

²⁴Seizure is a civil action against specific violative goods. FDA initiates a seizure by forwarding a seizure action to the U.S. attorney in whose judicial district the violative goods are located. The U.S. attorney files a Complaint for Forfeiture with the U.S. district court, which then issues a motion and warrant directing seizure of the goods. In this instance, U.S. marshals, accompanied by FDA investigators, seized adulterated heparin sodium and heparin lithium in November 2008 that was being held under quarantine at the firm. According to FDA, the U.S. Marshals found that the inventory of this quarantined product was consistent with inventories conducted during previous inspections by FDA in May and September 2008, and the seized heparin remained in quarantine at the firm until it was removed and destroyed by a contracted waste management company in March 2009.

²⁵According to FDA officials, limited inspections are narrow in scope and do not include a full assessment of all GMP provisions. Officials said that most GMP problems are likely to be cited at downstream manufacturing facilities, such as the production site of APIs or finished drug products, due to more stringent GMP expectations, including increased testing, manufacturing, and overall quality assurance requirements.

²⁶FDA classifies inspections as NAI if no objectionable conditions or practices were found during the inspection (i.e., conditions or practices that violate current good manufacturing practices), or if the significance of the documented objectionable conditions found does not justify further FDA action. Other FDA inspection classifications include voluntary action indicated (VAI) and official action indicated (OAI). A classification of VAI means that objectionable conditions were identified but any corrective actions are left to the establishment to take voluntarily. A classification of OAI means that objectionable conditions were found that warrant regulatory action by FDA.

Officials also told us that at least one of these firms was not shipping crude heparin directly to the United States; however, FDA's import data show that both firms shipped crude heparin directly to the United States in 2006, which, according to retrospective testing conducted in 2008 by SPL, Baxter's API manufacturer, is when OSCS contamination of SPL's heparin supply was first detected.²⁷ Additionally, officials told us that no GMP violations were observed during these limited inspections, but acknowledged in congressional testimony that inspectors were not able to observe the laboratory of one of the firms. Overall, FDA officials told us that in both instances the agency did not have sufficient evidence to put the two consolidators on import alert and that, with some exceptions, a firm's refusal to allow for a complete inspection is not itself one of the bases for product detention at the U.S. border.

Additionally, FDA learned that China's State Food and Drug Administration had sealed some firms' heparin and had instructed the firms not to open these seals. This prevented at least one firm from conclusively determining which of its crude suppliers were associated with OSCS contamination, which FDA learned of during a preapproval inspection of this particular firm. According to FDA officials, FDA was concerned that this firm was unable to complete its investigation of suppliers and requested a reinspection of the firm. From the reinspection, which took place approximately 1 year later, the agency determined that the firm had implemented testing methods to detect OSCS contamination, communicated its expectations and requirements to its suppliers, and increased the frequency of its supplier audits. FDA also learned during the reinspection that the firm had completed its testing, which resulted in the permanent disqualification of two of its suppliers.

FDA officials said that they are continuing to take steps to improve the quality of drugs manufactured outside of the United States. In addition to creating and staffing FDA posts overseas, FDA officials told us that the agency has established a cadre of FDA's U.S.-based investigators to conduct foreign drug inspections throughout the world as needed. FDA is also increasing the size of its cadre of the highest-certified drug inspectors to assist with foreign inspections, and increasing the number of translators

²⁷More recently, FDA conducted a pre-approval inspection of SPL, which was completed in September 2010, and cited the firm for its failure to fully investigate a complaint the firm received after the heparin crisis regarding contaminated heparin. FDA officials told us that the heparin involved in this case was initially manufactured and distributed in late 2006 and 2007.

it brings on foreign inspections, especially to China. FDA officials told us that the agency continues to emphasize the responsibility of industry to ensure the safety and security of its supply chain, including placing emphasis on supply chain traceability during foreign drug inspections. In addition, according to officials, FDA also continues to revise its inspection and surveillance programs to focus on higher-risk facilities and products. For example, officials told us that in fiscal year 2010 the agency developed and used a risk-based model and other information to focus its annual surveillance sampling program—a long-standing FDA program to sample drug components offered for import, which changes focus annually—on APIs potentially susceptible to economically motivated adulteration.

FDA Worked with Heparin Manufacturers on Recalls of Contaminated Heparin Products while Ensuring an Adequate Heparin Supply for U.S. Consumers

Beginning in January 2008 when the first recalls of contaminated products occurred, FDA worked with manufacturers to ensure an adequate supply of uncontaminated heparin for the U.S. market. Weeks after Baxter initiated a recall of specific heparin lots associated with adverse reactions in patients, the company told FDA it wanted to recall almost all of its heparin products because the number of adverse reactions associated with its heparin continued to increase. FDA officials said they recognized that a large-scale recall could pose risks to U.S. patients if the remaining supply was not adequate to meet facilities' and providers' needs for heparin. Consequently, FDA engaged in discussions with APP, the other main U.S. heparin manufacturer, to determine the amount of heparin it had available and to determine if and when it could increase its heparin production to supply almost the entire U.S. market.²⁸ FDA and APP officials told us that APP's ability to increase production was initially limited and that FDA and APP worked together to increase APP's production capacity; for example, in July 2008, APP obtained permission from FDA to apply for an additional manufacturing facility—which FDA approved in October 2008—using a process that, according to APP officials, decreased FDA's approval time by months and allowed APP to begin releasing heparin manufactured at the

²⁸FDA also encouraged another manufacturer at this time to submit an application for a generic heparin product to further mitigate a potential shortage, and granted expedited review to this additional manufacturer's application. FDA officials told us that other generic drugs granted expedited review, such as drugs for the President's Emergency Plan for AIDS Relief, typically take about 6 months to approve. However, despite the expedited designation, the approval process for this particular application took 18 months, so this product was not available until well after the crisis period ended. FDA officials explained that the decision on this approval took longer than usual to ensure that the agency's approach to approval criteria for generic heparin products was scientifically appropriate.

alternate site and subsequently list it as an approved facility with the agency.

During this time, FDA worked with Baxter to manage the risks of the contaminated heparin that remained on the U.S. market and postpone the expanded recall of almost all Baxter heparin products until the agency was sure that APP could increase its heparin production to meet the needs of U.S. patients, thus avoiding a shortage of a medically necessary drug. According to FDA officials, FDA and Baxter worked together to develop a risk management plan, and FDA issued a public health advisory to inform the public of serious adverse events and recommend measures—such as using the lowest necessary dose, administering the heparin as slowly as acceptable, and monitoring patients closely for adverse events—to help minimize these risks in instances where Baxter heparin was the only product available.

FDA continued monitoring for the possibility of a heparin shortage even after APP told FDA it could increase production. FDA continued to be concerned about the adequacy of the U.S. heparin supply in the summer of 2008 due to a shortage of raw materials in China and issues APP faced with its supply chain.²⁹ The agency also continued to work with manufacturers on product recalls. Overall, FDA worked with 15 other drug and device firms to recall at least 11 drug products and 72 medical device products as a result of the heparin crisis.

²⁹According to information compiled by FDA investigators, the number of pig farmers in China had decreased by 40 percent over the 5 years prior to the crisis because of economic and agricultural trends. The availability of raw materials for heparin was further limited after the crisis because many crude manufacturers were found to have OSCS contamination. Additionally, investigators reported that a major earthquake—which killed an estimated 3.1 million pigs in Sichuan Province—and blue ear pig disease contributed to the potential shortage of materials. FDA continued to monitor the adequacy of the U.S. heparin supply because of these issues and because APP reduced its number of qualified API suppliers after it agreed to increase production to meet the demand of the entire U.S. market.

FDA Collaborated with Its International Regulatory Partners to Exchange Information and Help Prevent Future Crises, but Could Not Determine the Original Source of OSCS Contamination

FDA reached out to its international regulatory partners during the crisis to exchange information about contaminated heparin, but was ultimately unable to identify the original source of contamination. In early February 2008, prior to FDA's public announcement about the adverse events seen in the United States, FDA told its partners—which included regulatory agencies in 17 countries, the European Commission, and the European pharmaceutical regulatory agency—about these adverse events and asked them to share information on any similar events related to heparin.³⁰ By March 2008, FDA was aware of at least 10 countries, including the United States, that had found OSCS contamination in their heparin supply. However, only 1 other country, Germany, also observed an increase in heparin-associated adverse events.³¹ Through its communications with other countries, FDA learned that some Chinese manufacturers associated with contamination in these countries also supplied heparin to the U.S. market. Notably, one of these manufacturers was the primary supplier for APP, the U.S. firm that supplied almost the entire U.S. heparin market after Baxter recalled its products. In this instance, FDA responded to this information by conducting an investigation of the manufacturer and as a result concluded that the heparin distributed by APP in the United States was not contaminated.

FDA also collaborated with the Chinese government during the crisis, though FDA was ultimately unable to determine the original source of contamination. According to FDA officials, FDA's preliminary investigation concluded that contamination did not take place in the United States. As a result, FDA requested jurisdiction from the Chinese government in order to conduct a criminal investigation in China to determine the source of contamination. However, Chinese officials would

³⁰An FDA official told us that existing agreements with other countries stated that FDA could notify regulatory agencies in these countries of the adverse events associated with heparin in the United States before the agency made this information public. Of the 17 countries with which FDA communicated, the agency had confidentiality commitments with all except China; however, the official said that the agency notified China of these adverse events as well because of the terms of an existing memorandum of agreement.

³¹Experts believe that an increase in heparin-associated adverse events was seen only in some countries for various reasons, such as differences in the type of heparin used and the way in which heparin is administered. For more information, see appendix I.

not grant this request and denied that contamination took place in China.³² Through retrospective testing of retained heparin samples conducted by firms in 2008, FDA learned that OSCS-contaminated crude heparin had been introduced into the global heparin supply as early as May 2006. FDA investigators believe that OSCS was increasingly added to heparin by Chinese establishments that manufacture crude heparin so that the establishments could cut costs.

Although unable to collaborate with the Chinese government in a formal criminal investigation, FDA has continued to collaborate with its international partners to avoid similar crises in the future. For example, FDA organized an international conference in April 2008 during which regulators and academics from 10 additional countries around the world, including China, along with the standard-setting entities for pharmaceuticals in the United States and Europe, shared information on their experiences with contaminated heparin during the crisis and discussed potential steps to prevent future contamination incidents. The agency also participates in the API Pilot Program with the regulatory bodies of Europe and Australia. According to FDA officials, drug regulatory agencies in this program—which began after the heparin crisis—share and obtain information about API inspections they conduct around the world to better leverage their inspection resources. Officials said that FDA’s establishment of overseas offices will also help facilitate collaboration between FDA and foreign regulatory agencies.

³²In December 2007, prior to FDA’s knowledge of increased adverse events associated with heparin, the U.S. Department of Health and Human Services and China’s State Food and Drug Administration (SFDA) entered into a memorandum of agreement (MOA) in which both countries agreed to engage in regulatory cooperation regarding improving the authenticity, quality, safety, and effectiveness of drugs. The MOA, however, only includes API and not crude material in its definition of a drug. FDA investigators told us they were denied access to some of the Chinese workshops that supplied crude heparin manufacturers. FDA officials also told us that FDA and other U.S. government officials contacted China’s Ministry of Public Security (MPS) in June 2008 to request consideration of a joint criminal investigation. MPS told the U.S. officials that FDA would need to first request a referral from China’s SFDA to receive jurisdiction to investigate in China. However, FDA’s request for a referral was declined by SFDA. According to FDA officials, SFDA told FDA that it did not have jurisdiction over Chinese exports and did not have any law enforcement capabilities. Chinese officials told FDA officials that contamination did not happen in China. FDA officials told us that they are aware of domestic heparin recalls in China that took place after SFDA ordered that all Chinese heparin undergo testing to detect OSCS.

FDA Coordinated Resources to Respond to the Heparin Crisis, but Did Not Adequately Address Risks Related to Working with Certain External Entities

FDA coordinated internal and external resources to respond to the contaminated heparin crisis, but did not adequately address risks related to working with certain external entities with ties to heparin firms. Not adequately addressing these risks could have affected the public's confidence in FDA's response efforts and in its other activities related to the regulation of heparin products and also left FDA open to claims for payment for services that these external entities provided to FDA on a voluntary basis.

FDA Coordinated Internal Resources to Respond to the Heparin Crisis and Plan for Future Crises

In responding to the heparin crisis, FDA coordinated response efforts in accordance with its ERP and developed a new *Emergency Operations Plan* (EOP) to guide its response to future crises. According to FDA officials, OCM initially coordinated the agency's response efforts, which included many of FDA's offices and centers. FDA officials said the total number of centers, offices, and divisions within the agency that were involved in responding to the contaminated heparin crisis was over 40 (see app. II for a complete list of FDA centers, offices, and divisions that were involved in the heparin crisis). On February 8, 2008, CDC reported that the problem was with the heparin drug product and not with medical devices as was originally thought.³³ Once this link was made, FDA officials determined that CDER would be best equipped to lead scientific efforts to identify the contaminant.

According to FDA officials, there was no formal transition of leadership from OCM to CDER, but once the situation was discovered to be largely a drug issue, CDER increased its involvement and took over the role of lead coordinator from OCM. Once CDER assumed this responsibility, FDA no longer had an agency-level entity responsible for coordinating response efforts, and CDER coordinated the multiple centers and offices within the agency that continued to be involved in the crisis. CDER officials created a task force to coordinate the agency's response efforts across multiple centers, offices, and divisions. CDER's Heparin Task Force was initially composed of mostly CDER officials but expanded to involve some other FDA offices. The task force initially met daily and then weekly from

³³See CDC, Morbidity and Mortality Weekly Report, *Acute Allergic-Type Reactions Among Patients Undergoing Hemodialysis—Multiple States, 2007-2008* (Feb. 8, 2008).

February 25, 2008, through May 27, 2008. An FDA official said that information from the task force's meetings was dispersed to relevant staff throughout FDA through CDER's e-mail distribution list, which included over 200 FDA officials. OCM continued to be involved with CDER's task force by participating in task force meetings, but it did not have a role in the ongoing coordination of the agency's efforts to respond to the heparin crisis.

After the crisis, FDA conducted some lessons-learned meetings to focus on difficulties that occurred during the agency's response. Documentation from these meetings shows that agency officials believed that FDA staff showed remarkable dedication during the crisis and that the agency was successful in removing contaminated products from and preventing the introduction of further contaminated product into the market place. However, these documents also show that there were some areas in which the agency's response could have been improved. Specifically, these documents indicate that the lack of details in the ERP and the absence of coordination at the agency level for the duration of the crisis may have led to some process delays and difficulty with internal and external communication. For example, CDER officials stated in a lessons-learned document that the agency's response to future crises could benefit from guidance that clearly delineates who should lead the agency's efforts during a crisis. According to this document, CDER officials said that it was not clear who, OCM or CDER, should lead the agency's efforts, since the ERP was not specific about who should coordinate the agency's response during a crisis. Additionally, when leadership transitioned to CDER, center officials had to spend time determining leadership roles within the center. In another lessons-learned document, CDRH officials said that external communication was sometimes complicated by CDER being the lead office. Specifically, issues related to heparin-containing medical devices were not always included in CDER-led task force discussions and were consequently often not addressed in CDER's communications with the public, other countries, or industry.

FDA officials told us that the agency has been working since October 2008 on the development of the new EOP, which is intended to address some of the difficulties encountered during previous crises, including lack of specific details on agency coordination. According to FDA officials, the new EOP was finalized in September 2010 and replaces the agency's existing ERP. FDA officials also told us that the new EOP is based on guidance from the National Response Framework and will incorporate principles of emergency operation—including the National Incident Management System and the Incident Command Structure—that are

designed to help agencies better coordinate efforts in the event of an emergency.³⁴ According to these officials, the EOP will be more detailed in terms of coordination within the agency and clearer about roles and responsibilities of centers and offices in any emergency, large or small, that the agency may face.³⁵ For example, the new EOP is to contain a section devoted to coordination at the agency level within FDA's headquarters. This section will offer guidance and a specific coordination structure that agency officials can use during an incident to help ensure that response resources and capabilities from multiple centers and offices within the agency are well organized. The EOP is to also include two new coordinator positions—the Agency Incident Coordinator (AIC) and the Agency Executive Group (AEG)—to facilitate agency-level coordination of an incident. According to this official, the role of the AIC will be to manage an incident at the agency level and to serve as a communication bridge between the Commissioner's Office and staff in the agency's centers and offices responding to an emergency. The AEG will be a group of senior-level executives at FDA who will provide strategic policy direction and guidance for major emergency response activities. The AEG is expected to approve important policy decisions in consultation with the AIC and the Commissioner of FDA.

³⁴The National Response Framework is a guide developed by the U.S. Department of Homeland Security that details how the first-response entities across the country conduct all-hazards response—from the smallest incident to the largest catastrophe. It is built upon scalable, flexible, and adaptable coordinating structures to align key roles and responsibilities across the nation, linking all levels of government, nongovernmental organizations, and the private sector.

³⁵The new plan provides guidance for three operational levels of agency response: routine, increased, and escalated. For example, a report of a single person's illness, injury, or consumer complaint with no or very few similar complaints in FDA systems would typically call for a routine response from the agency with normal staffing and regular work hours. Whereas an event such as Hurricane Katrina or the heparin crisis would lead to an escalated response in which additional support personnel and subject-matter experts might be needed and would be working 24 hours a day, 7 days a week.

FDA Coordinated External Resources to Respond to the Crisis, but Did Not Adequately Address the Risks of Working with Certain External Entities

FDA worked with several external scientists during the heparin crisis, but did not address certain risks that engaging two of these scientists, and additional external entities engaged by one of these scientists, posed to the agency. In February 2008, FDA officials contacted five external scientists, including one who was employed by the agency as a special consultant, for assistance with the heparin crisis, and FDA worked with these scientists for varying time periods.³⁶ Agency officials told us that they sought the advice of these external scientists because the agency lacked the necessary instrumentation and expertise to identify and develop new testing methods to detect the specific contaminant. According to FDA officials, these external scientists were engaged to provide the agency with technical and factual scientific advice related to the identity of the unknown contaminant and tests to identify this contaminant, and all policy judgments and decisions related to this advice were made by CDER officials. FDA communicated with external scientists frequently during the height of the crisis period and told us that some of these scientists were brought together for at least two in-person meetings to share and discuss their individual findings.

All five scientists worked directly with FDA, but they did not all have the same working arrangements with the agency. One of the scientists was a participant in FDA's Science Advisor Program and was considered an FDA employee.³⁷ Two of the scientists were employees of a university with which FDA contracted for testing of heparin samples; the university was selected in part because of its close proximity to FDA's Division of Pharmaceutical Analysis and the availability of advanced instrumentation and staff expertise necessary for testing. The two remaining scientists that FDA contacted in late February were not employees of FDA or FDA contractors. The agency characterized these scientists as volunteers and told us that they had been informally identified by CDER staff as experts in heparin analysis. FDA officials said that these two scientists provided services on an uncompensated basis in response to the oral requests of

³⁶FDA contacted these five scientists at different times throughout the month. The agency began heparin-related work with three of the scientists in early February and engaged the other two scientists in late February. The agency also continued to work with these five scientists for varying time periods. For example, one scientist told us that his work with the agency ended in April 2008, two of these scientists told us that their work with the agency continued through May 2008, and one scientist told us that his work with the agency continued until at least September 2008.

³⁷This scientist was appointed under section 209(f) of title 42, United States Code, which provides for the appointment of special consultants without regard to the civil service laws.

CDER staff. With FDA's knowledge, one of these two scientists obtained assistance in his work for FDA from external entities, including a drug development firm and an Italian research institute, also on an uncompensated basis.

The two scientists characterized by FDA as volunteers had professional and financial ties to heparin firms. Both served as paid consultants to two of the primary firms associated with contaminated heparin. In addition, one of the scientists was a cofounder and member of the board of directors, as well as an equity interest holder, in a third firm, which, at the time of the crisis, had a pending application for a heparin product before FDA. The agency allowed this scientist to obtain assistance in conducting analytical work to identify the contaminant in heparin from this firm despite its pending application for a heparin product.³⁸ This drug manufacturer dedicated approximately 30 staff members from its analytical and biology groups for periods ranging from a few weeks to 3 months to assist in the effort to identify the contaminant in heparin.

FDA's internal guidance, *The Leveraging Handbook*, addresses risks that may be presented in collaborative arrangements with external entities. The handbook cautions FDA employees to weigh certain legal and ethical considerations when entering into partnerships and references rules applicable to the behavior of individual employees, but also identifies other principles, which it characterizes as "institutional ethics."³⁹ These prudential considerations are designed to prevent public perception concerns and to demonstrate that the agency has established procedures designed to display that it is worthy of public trust. Among other things, the guidance cautions staff to consider the ethical implications of accepting gifts for the agency from external entities, stating that the agency should be judicious in accepting gifts to avoid the appearance that

³⁸The application, which was pending at the time that this firm provided uncompensated services in support of FDA's effort to identify the contaminant, was approved in July 2010. FDA officials stated that its collaboration with this scientist had no impact on the agency's decision regarding the application.

³⁹In response to our inquiries, FDA identified *The Leveraging Handbook* as a source of guidance with respect to consultants and experts. Although the working arrangements addressed in the handbook are more formal arrangements than those used with the external scientists with ties to heparin firms, the ethical principles included in this guidance would be applicable to the informal arrangements with these scientists during the heparin crisis.

its programs or operations may be compromised.⁴⁰ Specifically, staff are to balance the importance of a potential gift to the agency against the potential appearance problems that may be caused by acceptance of the gift. Steps to be considered in the balancing test include determining if accepting the gift would reflect unfavorably on the agency's ability to carry out its responsibilities in a fair and objective manner and whether the acceptance of a gift would compromise the integrity of, or the appearance of the integrity of, a program or official. Staff are also asked to determine the value to the agency of accepting the gift and the extent to which it will enable the agency to accomplish its mission. Further, *The Leveraging Handbook* instructs staff to consider the nature and sensitivity of matters pending before the agency that would affect the interests of the gift donor and to weigh the agency's interest in accepting the gift against any actual or apparent conflict of interest. Finally, the guidance provides for consideration of whether the gift would be from a prohibited source if the gift were made to an individual employee and calls for gifts from prohibited sources to be subject to higher scrutiny.⁴¹

FDA officials were aware of the scientists' ties to heparin manufacturers, but did not take adequate steps to consider whether these relationships exposed the agency to the risks described in its guidance or to address these risks before engaging them. FDA officials told us that they believed that there was insufficient time to address these ties in the midst of the heparin crisis and that the CDER staff who identified these scientists were confident that they could independently assess the input from these scientists through robust, detailed, and transparent discussions; they said that this would address any appearance problems related to the scientists' input. FDA officials also emphasized that the agency made all policy judgments and said that they disclosed the work of these scientists to the public through peer-reviewed journal articles in late April, after the specific contaminant in heparin was identified.⁴² However, FDA officials told us that they did not take steps before accepting voluntary services of

⁴⁰FDA officials told us that the agency exercised its authority to accept gifts in accepting the services of these scientists in this situation.

⁴¹Prohibited sources include a person or organization that conducts activities regulated by the agency or seeking official action by the agency. See 5 C.F.R. § 2635.203(d) (2010).

⁴²See T. K. Kishimoto, et al. "Contaminated Heparin Associated with Adverse Clinical Events and Activation of the Contact System," *New England Journal of Medicine*, vol. 358, no. 23 (2008) and M. Guerrini, et al. "Oversulfated Chondroitin Sulfate Is a Contaminant in Heparin Associated with Adverse Clinical Events," *Nature Biotechnology*, vol. 26, no. 6 (2008).

these scientists to assess whether their ties to firms associated with contaminated heparin would compromise the integrity of FDA's activities, or the appearance of integrity, so as to undermine the public perception of FDA's management of the heparin crisis.⁴³ Nor is there evidence that they considered whether the agency's acceptance of voluntary services from a scientist with an interest in a firm with an application pending before FDA, along with employees of that firm, would compromise, or appear to compromise, the agency's activities, including its activities related to the approval of heparin products. Moreover, FDA did not fully disclose the existence or extent of these scientists' interests while they were providing assistance or afterwards.⁴⁴ CDER staff did not consult with the Office of Chief Counsel or agency ethics officials about their working arrangements with these two scientists or seek advice as to whether the arrangements were consistent with the agency's ethics standards.

FDA's acceptance of voluntary services in connection with the heparin crisis also exposed the agency to the risk of claims for payment for the services provided. Federal agencies are generally prohibited from accepting voluntary services because of the risk of claims associated with them.⁴⁵ The statutory provision barring the acceptance of these services is best understood in the context of the preceding statutory provision, which prohibits agencies from incurring obligations in excess of their appropriations or before such appropriations are made.⁴⁶ The fundamental purpose of the voluntary services prohibition is to preserve the integrity of the appropriations process by preventing agencies from effectively incurring obligations in excess of or in advance of appropriations by accepting voluntary services with the expectation that Congress will recognize a "moral obligation" to pay for the services rendered.⁴⁷

⁴³According to FDA, the agency's main concern about engaging these experts was that their relationship with the pharmaceutical firms might limit their ability to participate in a free exchange of information with the agency. The agency reported that CDER officials took steps to ensure that the manufacturers agreed that their consultants could engage in free and open discussions with CDER staff.

⁴⁴For example, the published articles after the contaminant was identified did not fully disclose the assistance provided by the other entities or that the drug firm had a pending application for a heparin product before FDA. Further, no public disclosures were made while the scientists were providing assistance in identifying the specific contaminant.

⁴⁵31 U.S.C. § 1342 (2006).

⁴⁶31 U.S.C. § 1341 (2006).

⁴⁷See *Principles of Federal Appropriations Law*, vol. 2, 3rd ed., [GAO-06-382SP](#) (Washington, D.C.: February 2006), at 6-93-6-95.

Consistent with this underlying purpose, voluntary services have been defined as those that are not rendered under a prior contract or advance agreement that they will be gratuitous and are, therefore, likely to form the basis of future claims against the government.⁴⁸ However, the acceptance of services that are offered as gratuitous—that is, with no expectation of payment—with a record made of that fact, does not violate the voluntary services prohibition.⁴⁹ Such services do not give rise to any obligation or financial liability and therefore do not expose an agency to the risk of claims for payment.

FDA officials told us that the agency was authorized to accept voluntary services during the heparin crisis under an emergency exception and therefore was not required to obtain a written agreement that the services were offered with no expectation of payment. The statute provides an exception for emergencies involving the safety of human life or the protection of property, which the statute defines as circumstances involving an imminent threat to the safety of human life or the protection of property.⁵⁰ FDA officials explained that the sharp increase in reports of severe allergic reactions to heparin in late January 2008 signaled a public health emergency requiring the agency to quickly identify and assemble the scientific expertise of those who could help identify the source of the crisis in order to protect patients and ensure the safety of a medically

⁴⁸B-204326, July 26, 1982.

⁴⁹27 Comp. Dec. 131, 132-133 (1920) (The voluntary services prohibition was intended to guard against claims for compensation, and a service offered clearly and distinctly as gratuitous with a proper record made of that fact does not violate the statute.) More recently, the Department of Justice explained that the voluntary services prohibition was intended to eliminate subsequent claims against the United States for compensation of the “volunteer,” rather than to deprive the government of truly gratuitous services. 6 Op. Off. Legal Counsel 160, 162 (1982).

⁵⁰Prior to 1990, the statutory provision referred only to “emergencies involving the safety of human life or the protection of property.” In response to an opinion of the Attorney General regarding agencies’ authority to incur obligations during a temporary lapse in appropriations, 43 Op. Att’y Gen. 293 (1981), Congress amended the voluntary services prohibition to limit agency activities and related obligations to extreme circumstances: “[A]s used in this section the term ‘emergencies involving the safety of human life or the protection of property’ does not include ongoing, regular functions of government the suspension of which would not imminently threaten the safety of human life or the protection of property.” Pub. L. No. 101-508, § 13213(b), 104 Stat. 1388, 1388-621 (1990); H.R. Conf. Rep. No. 101-964, at 1170 (1990) (the statutory change was intended to “guard against what the conferees believe might be an overly broad interpretation of [the Attorney General’s opinion] regarding the authority for the continuance of Government functions during the temporary lapse of appropriations, and affirm that the constitutional power of the purse resides with Congress.”).

necessary drug. By late February 2008, FDA had developed a screening method to distinguish contaminated heparin from uncontaminated heparin, but had not identified the precise contaminant or developed specific methods of testing for this specific contaminant, and obtained the voluntary services of additional scientists for this purpose.⁵¹

While the existence of an emergency would provide a legal basis for agencies to accept voluntary services, it would not protect them from subsequent claims for payment. To the contrary, the acceptance of services under the emergency exception would give rise to obligations—that is, financial liabilities—for which claims for payment could be made.⁵² As noted above, however, agencies accepting services in an emergency or otherwise may guard against claims for compensation by establishing that the services are gratuitous and, as such, do not give rise to any obligation or financial liability on the part of the government. This is accomplished by obtaining a written agreement from those providing services that they will receive no compensation and waive any future claims against the government for their services.⁵³

⁵¹In describing its use of external entities during the heparin crisis, FDA did not disclose why these scientists were engaged as volunteers and others, engaged earlier, were not, or why services of a voluntary nature were necessary in late February 2008 to protect heparin users from an imminent threat given the steps that the agency had already taken, including the development of a preliminary screening method to distinguish contaminated heparin from uncontaminated heparin and recalls of contaminated heparin.

⁵²*Cf.* OMB Circular No. A-11, *Preparation, Submission, and Execution of the Budget*, § 124.3 (agencies may incur obligations for essential activities necessary to protect life and property during a lapse in appropriations); Memorandum for the Director of the Office of Management and Budget, *Government Operations in the Event of a Lapse in Appropriations*, August 16, 1995 (the emergency exception authorizes agencies to enter into obligations, but does not by itself authorize paying employees in emergencies); 43 Op. Att’y Gen. 293, 306 (“Congress has contemplated expressly . . . that emergencies will exist that will justify incurring obligations for employee compensation in advance of appropriations . . .”).

⁵³*See, e.g.*, B-302811, July 12, 2004. In that decision, we addressed a contract under which real estate brokers agreed to provide services at no cost to the General Services Administration (GSA) with the understanding that they would be compensated by commissions from landlords. We noted that the acceptance of services without payment pursuant to a valid, binding “no-cost contract” did not augment GSA’s appropriation or violate the voluntary services prohibition because the agency had no financial liability to the brokers and the brokers would have no expectation of a payment from GSA; if a landlord were to fail to pay a broker, the broker would have no claim against GSA.

FDA did not take steps to establish that the services provided by two of the external scientists, as well as the services obtained by one of those scientists from two other entities, imposed no obligation or financial liability and, in this respect, exposed the agency to the risk that claims for compensation would be made for which funds were not available. Regardless of whether the circumstances that existed when FDA contacted these scientists constituted an emergency, they did not preclude the agency from addressing this risk.⁵⁴ To the extent that time was of the essence, a letter from those providing services to the agency would have been sufficient; there is no detailed or prescribed form for the provision of gratuitous services. In addition, the provision of services was not unexpected—the agency requested and discussed the services provided by the selected scientists as part of the ongoing process of resolving the heparin crisis. By late February 2008, the agency had overseen a recall of heparin products and determined how to distinguish contaminated heparin from uncontaminated heparin using a preliminary screening method. FDA requested the services of the two scientists to help it identify the specific contaminant and develop appropriate testing methodologies for its detection, and these scientists provided analyses and opinions to FDA over a period of several weeks. FDA officials told us that determining the precise identity of the contaminant and developing appropriate testing methodologies were necessary to resolve the crisis and that the services provided and arranged for by the two scientists were critical for doing so. However, those facts do not explain why FDA did not take appropriate steps to protect the agency from the financial exposure arising from services that it had both requested and accepted.

Voluntary services may be accepted where otherwise authorized by law, and FDA also cited the agency's authority to accept gifts as the basis for its acceptance of voluntary services without a written agreement in connection with the heparin crisis.⁵⁵ A gift is generally understood to be a gratuitous conveyance without any consideration, the essential elements

⁵⁴Cf. B-310108, Feb. 6, 2008 (dire circumstances did not preclude the Forest Service from using expedited reapportionment procedures to avoid the overobligation of its apportionment for wildland fire management).

⁵⁵FDA stated that the agency has express authority to accept gifts of services and cited section 238 of title 42, United States Code. Section 238 authorizes the Secretary of Health and Human Services to accept on behalf of the United States "gifts made unconditionally by will or otherwise for the benefit of the [Public Health] Service or for the carrying out of any of its functions."

of which are acceptance, delivery, and the intent to make a gift.⁵⁶ By definition, a gift does not give rise to any obligation or liability and poses no risk of subsequent claims for compensation. We do not address the scope of the provision cited by FDA, but note that it does not expressly authorize gifts of services and contemplates that gifts be made by means of some instrument. As discussed above, however, there is no evidence to establish that the external scientists intended to provide their services on a gratuitous basis—that is, to donate their services and the services of others to the agency—that would protect the agency from such claims.

FDA Monitored and Analyzed Adverse Events Associated with Heparin, but It Was Unable to Link Them to Contaminated Heparin

FDA increased its monitoring of adverse events, including deaths, associated with heparin and conducted analyses. FDA was unable to link any of the adverse events to contaminated heparin because it was unable to establish a causal relationship due to data limitations and confounding factors involving the individual patients.

FDA Increased Its Monitoring of Adverse Event Reports Associated with Heparin by Working with Manufacturers and Dedicating Staff Resources

FDA increased its monitoring of adverse event reports by working with heparin drug and device manufacturers to expedite submission of these reports to FDA. According to FDA officials, FDA contacted Baxter in February 2008 to request early submission of its adverse event reports associated with heparin and requested reports from two other heparin manufacturers, APP and Hospira, later in March 2008. FDA officials said that these reports would otherwise have been due later in the year. A few weeks later, in April 2008, FDA sent a letter to almost 100 manufacturers and distributors of medical devices that contained or were coated with heparin. In this letter, FDA required these firms to submit all reports of heparin-related adverse events within 5 work days of the firm becoming aware of these events, in accordance with federal regulations.⁵⁷ This requirement remained in effect for 120 days of the date of the letter from FDA.

⁵⁶B-274855, Jan. 23, 1997.

⁵⁷See 21 C.F.R. § 803.53(b) (2010).

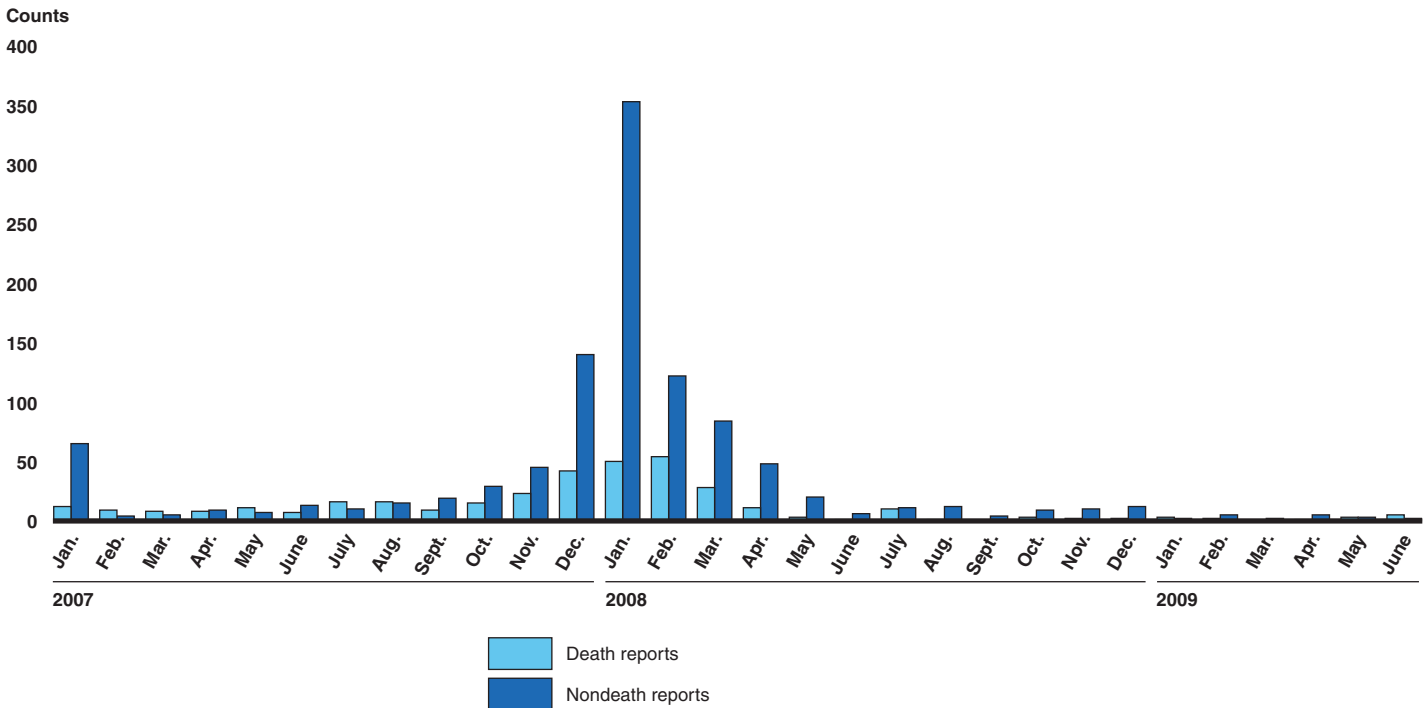
FDA also monitored trends in the number of reports of adverse events associated with heparin drug products and heparin-containing medical devices that FDA received before, during, and after the crisis. FDA dedicated staff to manage the increased number of heparin-specific reports that the agency received during the crisis and to conduct searches of its AERS and MAUDE databases to retrieve additional related reports that had already been submitted to FDA prior to the crisis. FDA officials said that retrieving and entering information from AERS and MAUDE reports was extremely time and resource intensive in that information had to be entered manually into spreadsheets and duplicate reports⁵⁸ had to be removed before the data could be analyzed.⁵⁹ FDA officials said that there was a certain baseline number of adverse event reports associated with heparin in 2007 prior to the heparin crisis and that the number of reports of adverse events associated with both heparin drug products and heparin-containing medical devices that FDA received decreased after the heparin crisis, returning to levels typically seen prior to the crisis.⁶⁰ For example, FDA received reports of 176 adverse events associated with heparin drug products that took place in February 2008, compared with 13 events that took place in February 2007 and 7 events that took place in February 2009. Figure 3 shows a breakdown of AERS reports of adverse events that resulted in death and reports that did not have a fatal outcome (nondeaths) from January 2007 through June 2009.

⁵⁸FDA officials explained that they sometimes received adverse event reports from consumers or health care professionals as well as manufacturers regarding the same event.

⁵⁹FDA officials told us that the agency continues work to replace AERS with the new FDA Adverse Event Reporting System (FAERS). FAERS is intended to make retrieval and analysis of adverse event and death data more efficient and will contain software that would make analysis of safety signals closer to real time.

⁶⁰FDA also posted and updated the number of adverse events, which resulted in death, associated with heparin drug products, submitted to AERS from January 1, 2007, through May 31, 2008, on its Web site to respond to media requests. These numbers showed that reports of deaths had decreased since contaminated heparin was recalled from the U.S. market; however, FDA was unable to determine the contamination status of the heparin associated with most of these reports.

Figure 3: Reports of Adverse Events in Patients Who Were Administered Heparin Drug Products, January 2007–June 2009



Source: FDA.

Notes: The death and nondeath reports in the figure are from AERS reports, which were submitted to FDA by consumers, health care professionals, and product manufacturers. According to FDA, the numbers of reports are crude counts; duplicate reports have not been identified and removed. A formal causality analysis was not performed on all of these cases.

The numbers of death and nondeath reports in the figure reflect the date the adverse event occurred. However, when only the year of an event is known, AERS assigns a default event date of January 1 of that year. Reports that provide no information at all related to when the event occurred are not assigned any event date and the AERS event date field is left blank. According to FDA, for January 2007, 57 of the 65 nondeath reports and 2 of the 12 death reports defaulted to January 1, 2007, and for January 2008, 106 of the 353 nondeath reports and none of the death reports defaulted to January 1, 2008. No reports in 2009 defaulted to January 1, 2009.

Regarding trends in adverse events in heparin-containing medical devices, during the crisis in March 2008, FDA conducted a search of the MAUDE database back to January 2005 through December 31, 2007. This search included all medical device products known to contain heparin using a search of terms in the report texts consistent with symptoms or signs with what was known about the contaminant, such as acute respiratory failure and nausea, and FDA identified 23 reports for that 3-year period. Using the same search term criteria, FDA identified 91 MAUDE reports from January 1, 2008, through August 31, 2008, and 16 reports from September 1, 2008, through September 1, 2009, indicating that the number

of reports associated with heparin-containing medical devices had decreased since the crisis.

FDA Analyzed Adverse Events Associated with Heparin and Heparin-Containing Medical Devices, but Was Unable to Link Them with Contaminated Heparin Due to Data Limitations and Confounding Factors Involving Patients

FDA conducted analyses of adverse events, including deaths, associated with heparin drug products and heparin-containing medical devices. To analyze adverse events associated with heparin drugs, FDA reviewed a total of 701 AERS reports associated with heparin that the agency received from January 1, 2008, through March 31, 2008.⁶¹ Of the 701 reports, 675 were identified by searching AERS for allergic-type adverse events associated with heparin, such as a drop in blood pressure or acute respiratory failure, for both death and nondeath events. In its analysis of allergic-type adverse events associated with heparin, after excluding 101 allergic-type cases from this analysis, FDA included a total of 526 nondeath AERS reports and 48 death reports.⁶² FDA reported descriptive characteristics about this group of reports—for example, the average age of the patients; the manufacturer of the heparin drug product administered to the patients; if known, and the clinical setting where the heparin was administered. FDA also analyzed a total of 94 AERS reports of deaths associated with heparin, which included 68 allergic-type adverse events and an additional 26 death reports that were not identified as allergic-type adverse events.⁶³ FDA conducted further analyses of these reports using specific assessment criteria to determine whether they were caused by heparin, and concluded that three of the deaths were “probable or likely” linked with heparin. However, FDA did not know whether or not the heparin these patients received was contaminated because the lot numbers of the heparin that these patients received were not reported in the AERS reports.

⁶¹FDA identified the 701 reports, from which duplicate reports had been removed, based on an expanded case definition from the CDC investigation of allergic-type events in hemodialysis patients in January 2008 and specific search term criteria (see app. III for CDC’s case definition and FDA’s search term criteria).

⁶²The 101 allergic-type event cases were excluded based on specific criteria, including events that took place prior to January 1, 2007, and if the case had a clear alternative clinical explanation for the adverse event.

⁶³Of the 68 allergic-type death cases, 48 were also included in FDA’s analysis of allergic-type adverse events and 20 were part of the 101 allergic-type event cases that were excluded from the analysis of allergic-type events. FDA officials said that almost all of the death cases were reviewed regardless of their inclusion status in the allergic-type adverse events analysis. Seven death cases that occurred prior to January 1, 2007, and 1 death case that was a duplicate report were not included in FDA’s analysis of AERS death reports.

To analyze adverse events associated with heparin-containing medical devices, FDA reviewed a total of 143 MAUDE reports that the agency received from January 1, 2008, through August 31, 2008. FDA reviewed all of the MAUDE reports that FDA received associated with heparin-containing medical devices with an event date occurring during that time period.⁶⁴ Of the 143 reports, 128 were nondeath adverse events associated with heparin-containing medical devices, and the remaining 15 MAUDE reports had a death outcome. Three of these deaths were associated with medical devices known to contain contaminated heparin. FDA determined that these MAUDE reports of deaths were unlikely to have been caused by exposure to contaminated heparin, based on similar assessment criteria that FDA used with its analysis of the AERS death reports. (See app. III for FDA's death assessment criteria, and details of its AERS and MAUDE analyses.)

FDA's analyses of adverse events associated with both heparin and heparin-containing medical devices were constrained by data limitations. For example, FDA officials told us that the agency does not necessarily receive a report for every adverse event that occurs. For drug-related adverse event reports submitted to AERS, manufacturers are required to submit adverse event reports to FDA, but health providers and consumers are not required to do so but may submit such reports on a voluntary basis. For device-related adverse event reports submitted to MAUDE, importers, manufacturers, and user facilities (such as hospitals and nursing homes) are required to report certain device-related adverse events to FDA; others, including health professionals and consumers, may submit such reports on a voluntary basis.⁶⁵ In addition, many submitted reports do not include sufficient information to allow FDA to determine if a given report was associated with a contaminated product. FDA officials told us that they followed up on some of the reports of deaths included in the agency's AERS and MAUDE analyses by contacting the facility or individual that had submitted the report in an attempt to obtain additional information. Further, in our review of the 94 AERS death reports that FDA had analyzed, we found that only 13 reports included information on heparin lot numbers and 28 of the 46 voluntary reports did not list the heparin manufacturer. Consequently, it was not possible for FDA to

⁶⁴If a MAUDE report did not specifically have an event date listed, but was received by FDA between January 1, 2008, and August 31, 2008, it was conservatively assumed to have occurred during that time frame and included in the MAUDE analysis.

⁶⁵See generally 21 C.F.R. §§ 314.80, 314.98, 803.1, 803.30, 803.40, 803.50 (2010).

determine the heparin contamination status in the majority of these deaths.

Further, even with complete information, it was difficult for FDA to link patient deaths to contaminated heparin because it was unable to establish a causal relationship due to the confounding factors of individual patients. For example, the FDA official who conducted FDA's analyses on adverse events associated with heparin-containing medical devices told us that it was hard to separate problems caused by the heparin contained within the medical device from symptoms or events related to the natural course of the underlying disease or condition, concurrently administered medications, or concurrent procedures. In addition, according to FDA officials, many of the patients that died were very sick and had complicated conditions that could themselves have caused the reported events, making it difficult to conclusively link their deaths to contaminated heparin.⁶⁶

Conclusions

FDA took various actions in response to the contaminated heparin crisis to help protect the public health. To help minimize the impact on U.S. consumers of heparin, the agency increased its oversight activities and monitoring of adverse events, worked with heparin manufacturers, and collaborated with its international partners. The agency increased its activities related to oversight of heparin firms by increasing the number of inspections and investigations and monitoring heparin imports, and worked with drug and device manufacturers to recall contaminated products while ensuring that an adequate supply of heparin was available. With the help of external entities, FDA identified the unknown contaminant and developed tests to screen heparin products. Agency officials also reached out to international regulatory partners during the crisis to exchange information about contaminated heparin and to help prevent future crises. Within a few months of the agency's increased efforts and cooperation with other entities, adverse events returned to precrisis levels.

While FDA took steps to protect the U.S. public from contaminated heparin, it did not take steps to consider and address risks associated with the way in which it engaged two external scientists and additional external

⁶⁶In our analysis of the 94 AERS death reports, we found that of the 78 reports that listed at least one condition for each patient, 63 of these reports listed multiple conditions.

entities engaged by one of these scientists. Although FDA has issued standards on collaboration with external entities in other contexts and governmentwide standards govern the acceptance of services free of charge, FDA did not take steps to ensure that these standards were considered and applied in connection with the heparin crisis. We believe that these standards can be applied in all situations in which the agency collaborates with external entities, including those situations in which time pressures exist. In accepting voluntary services from individuals with ties to heparin firms, including one that was affiliated with a company with a heparin drug product application before FDA for approval, agency officials ran the risk of undermining public confidence in the integrity of FDA's operations and of subjecting the agency to future claims for payment.

FDA is charged with protecting the health of the public from problems related to products that it regulates, and the agency works with external entities when necessary to ensure that it meets this goal. Because adulteration of FDA-regulated products could likely happen again, it is critical that the agency have clear and useful controls in place that it can apply in circumstances similar to those presented by the heparin crisis to help ensure that officials take appropriate steps to consider and address risks posed when engaging external entities.

Agency Comments and Our Evaluation

The Department of Health and Human Services (HHS) received a draft of this report and provided comments, which are reprinted in appendix IV. HHS also provided technical comments, which we incorporated as appropriate. In its comments, HHS described the challenges FDA faced when it first learned of severe allergic reactions suffered by dialysis patients during treatment. HHS described how FDA worked to protect the public from contaminated heparin while still ensuring that patients had access to a medically necessary drug. HHS said that FDA needed to identify and enlist the help of leading heparin experts to identify the contaminant in heparin. We agree that FDA faced numerous challenges in responding to the heparin crisis, including the need to obtain expert assistance. However, we also note the potential risks FDA faced in working with external scientists on a voluntary basis in the absence of appropriate controls—the risks of undermining public confidence in its efforts and of future claims for payment. Therefore, in our draft report, we recommended that FDA develop adequate controls to help avoid exposure to these risks when working with external entities in future situations similar to the heparin crisis. Specifically, we recommended that FDA develop a process for considering risks, including consulting with

appropriate offices within the agency; develop a process for documenting the steps taken to address risks; and disseminate guidance on these processes for its employees. FDA addressed the draft recommendation by issuing guidance on October 15, 2010, for FDA staff to follow when working with external scientific and other experts in emergency situations when the services are provided on a gratuitous basis.⁶⁷ The guidance includes a policy that is responsive to our recommendation, providing broadly for due consideration of risks that may be presented in collaborative arrangements with external entities, including conflicts of interest, as well as for documentation of decisions about addressing such risks. The guidance also includes specific procedures for the provision of gratuitous services, screening for conflicts of interest, and public disclosure.

In its comments, HHS also noted that FDA has learned from the heparin crisis to improve its processes for responding to emergencies. Specifically, FDA finalized its new Emergency Operations Plan to respond to future crises. HHS described various actions FDA took to protect the public health during the crisis and steps the agency has taken to safeguard the nation's heparin supply, including an increased number of inspections of heparin manufacturing and testing facilities related to the U.S. heparin supply. We had previously described these actions in the report. HHS also mentioned legislation currently under consideration by Congress that it believes will, if enacted, provide FDA with helpful tools to further secure the nation's drug supply chain, and ensure that the agency can hold industry accountable for the security and integrity of its supply chains and the quality control systems it uses to produce drugs for the American people.

As agreed with your office, unless you publicly announce the contents of this report earlier, we plan no further distribution until 30 days from the report date. At that time, we will send copies of this report to the Commissioner of FDA and appropriate congressional committees. The report is also available at no charge on the GAO Web site at <http://www.gao.gov>.

⁶⁷See *FDA Staff Manual Guides, Volume III—General Administration, External Relations, External Expert Gratuitous Services in an Emergency*, October 2010, <http://www.fda.gov/AboutFDA/ReportsManualsForms/StaffManualGuides/ucm229673.htm> (accessed October 19, 2010).

If you or your staff have any questions about this report, please contact me at (202) 512-7114 or crossem@gao.gov. Contact points for our Offices of Congressional Relations and Public Affairs may be found on the last page of this report. GAO staff who made major contributions to this report are listed in appendix V.

Sincerely yours,

A handwritten signature in black ink that reads "Marcia Crosse". The signature is written in a cursive style with a long horizontal flourish at the end.

Marcia Crosse
Director, Health Care

Appendix I: Technical Information about Contaminated Heparin

This appendix provides a brief review of the scientific research related to heparin contamination, focusing on peer-reviewed research articles published in January 2008 through January 2010.

What is heparin?

Heparin is an anticoagulant drug; that is, it prevents the formation of blood clots in the veins, arteries, and lungs. It is used before certain types of surgery, including coronary artery bypass graft surgery; in kidney patients before they undergo dialysis; and to prevent or treat other serious conditions, such as deep vein thrombosis and pulmonary emboli. Heparin is also used in medical devices—for example, blood oxygenators or catheters contain or are coated with heparin, and some diagnostic testing products, such as some capillary tubes, are manufactured using heparin.

Heparin is a natural product derived from animal tissue. Specifically, most heparin used in the United States is derived from the intestines of pigs. Pig intestines are processed into crude heparin, which is further refined into heparin active pharmaceutical ingredient (API), the active ingredient used in heparin drug products and devices. More than half of the finished heparin products in the United States and globally are made from Chinese-sourced materials.

The chemical makeup of heparin is complex. Because heparin is a drug derived from animal tissue, it is not a single chemical, but a mixture of many similar chemical chains of different sizes.

Two types of heparin are used in clinical practice: unfractionated heparin (UFH) and low molecular weight heparin (LMWH). The two forms of heparin differ in their molecular size and the route of administration: UFH is comprised of larger molecules than LMWH and is usually administered intravenously, while LMWH is usually administered subcutaneously (that is, injected under the skin). UFH is used often in the United States, whereas in Europe the predominant heparin is LMWH. Researchers and officials we interviewed said that the number of adverse events related to contaminated heparin may have varied by country because of these differences in the type of heparin administered and methods of administration, as well as because of differences in countries' adverse event reporting systems. In particular, one researcher explained that in the United States, physicians tend to administer a bolus dose of heparin, which is a faster method of administration but places patients at greater risk for a fatal drop in blood pressure.

What was the contaminant in contaminated heparin?

Food and Drug Administration (FDA) officials and their collaborators agreed that oversulfated chondroitin sulfate (OSCS) was a contaminant in the heparin that caused adverse events during the heparin crisis. FDA researchers and their collaborators showed that batches of heparin that had been associated with adverse events contained a contaminant.¹ They identified that substance as OSCS. Chemically, OSCS is similar to heparin, but OSCS is probably not a naturally occurring chemical. The researchers confirmed their identification by matching the contaminant to synthetic OSCS created by chemical modification of chondroitin sulfate, an inexpensive natural product used for the self-treatment of arthritis.

Other research articles have provided additional evidence that OSCS was present in contaminated heparin. For example, Clark et al. performed analysis on some contaminated heparin batches and concluded that the properties of the contaminant were consistent with those of OSCS.² Viskov et al. showed that the chemical properties of OSCS isolated from a batch of contaminated heparin were similar to those of synthetic OSCS.³ Finally, Zhang et al. examined samples of heparin from as far back as 1941 and identified the presence of OSCS in a sample from the U.S. market that was produced in 2008.⁴

LMWH heparin was also affected by OSCS contamination.⁵ Zhang et al. evaluated the sensitivity of OSCS to five different processes similar to

¹Marco Guerrini et al., "Oversulfated Chondroitin Sulfate is a Contaminant in Heparin Associated with Adverse Clinical Events," *Nature Biotechnology* vol. 26, no. 6 (June 2008): 669-675.

²M. Clark et al., "Molecular Profiling of Heparinase-I Resistant Glycosaminoglycans in Contaminated Heparins. Comparative Studies with Uncontaminated Heparin and Porcine Oversulfated Chondroitin Sulfate," *International Angiology* vol. 27, no. 5 (October 2008): 370-376.

³Christian Viskov et al., "Isolation and Characterization of Contaminants in Recalled Unfractionated Heparin and Low-Molecular-Weight Heparin," *Clinical and Applied Thrombosis/Hemostasis*, vol. 15, no. 4 (August 2009): 395-401.

⁴Zhenqing Zhang et al., "Analysis of Pharmaceutical Heparins and Potential Contaminants Using 1H-NMR and PAGE," *Journal of Pharmaceutical Sciences*, vol. 98, no. 11 (November 2009): 4017-4026.

⁵According to German researchers we interviewed, in Germany, one brand of LMWH was found to be contaminated, and a second brand was recalled in Europe.

ones used in preparing LMWH, and found that these processes varied in the extent to which they affected OSCS.⁶

The source of the OSCS contamination is still unknown, and researchers have proposed various hypotheses about the source of the OSCS contamination. For example, Fareed et al. suggested that the contamination of heparin with OSCS was not accidental, but was based on a rational design and prior knowledge of the chemical's molecular and anticoagulant profiles.⁷ Pan et al. conducted an analysis that detected additional under- and oversulfated contaminants in contaminated heparin and proposed that the OSCS present in the contaminated heparin batches could have come from an oversulfated form of a byproduct of the heparin production process, rather than derived from animal cartilage.⁸ Another study considered this hypothesis but concluded, based on analysis of oversulfated byproducts provided by Baxter (a major heparin manufacturer), that production byproducts were likely not the source of the OSCS found in contaminated heparin.⁹

How is the contaminant related to the adverse events?

CDC researchers found a link between adverse events and contaminated heparin.¹⁰ These researchers collected data related to the period November 2007 through January 2008 from 21 dialysis facilities that reported adverse events and 23 facilities that reported no adverse events. With these data, the researchers conducted a case-control study to test whether facility-level risk factors—such as the size of the facility, the type of heparin used at the facility, and the type of dialysis equipment used at the facility—were related to adverse events. They found a significant

⁶Zhenqing Zhang et al., "Oversulfated Chondroitin Sulfate: Impact of a Heparin Impurity, Associated with Adverse Clinical Events, on Low-Molecular-Weight Heparin Preparation," *Journal of Medicinal Chemistry*, vol. 51, no. 18 (2008): 5498-5501.

⁷Jawed Fareed et al., "Biological Profile of the Hyper/Oversulfated Chondroitin Sulfate Contaminant Isolated from Recalled Heparin," *Seminars in Thrombosis and Hemostasis*, vol. 34, no. supplement 1 (2008): 119-127.

⁸Jing Pan et al., "Oversulfated Chondroitin Sulfate Is Not the Sole Contaminant in Heparin," *Nature Biotechnology*, vol. 28, no. 3 (March 2010): 203-207.

⁹Marco Guerrini et al., "Orthogonal Analytical Approaches to Detect Potential Contaminants in Heparin," *PNAS*, vol. 106, no. 40 (October 6, 2009): 16956-16961.

¹⁰David B. Blossom et al., "Outbreak of Adverse Reactions Associated with Contaminated Heparin," *New England Journal of Medicine*, vol. 359, no. 25 (December 18, 2008): 2674-2684.

association between the number of adverse events reported by facilities and their use of Baxter heparin. They reported that the type of adverse reactions experienced by patients who received contaminated heparin varied, but often included low blood pressure and nausea. The researchers could not estimate the percentage of patients who experienced adverse reactions after receiving contaminated heparin because the total number of patients in the United States who received heparin during this period is unknown.

In other articles, researchers have proposed possible biological mechanisms by which OSCS could have caused the observed adverse events.¹¹ Researchers have also suggested that exposure to OSCS could have effects beyond the acute allergic reactions reported during the heparin crisis. For example, one article showed that patients who received dialysis at a university in the United States in 2008 had more of a specific type of antiheparin antibody in their blood than patients who received dialysis in 2006 and 2007, indicating that OSCS may cause an immune response not seen with uncontaminated heparin.¹² Similarly, other researchers have presented data showing that the incidence of heparin-induced thrombocytopenia, a type of immune reaction to heparin, increased in Germany during the contaminated heparin crisis.¹³

How is the contaminant detected?

The standard for heparin testing now includes two tests for OSCS. In October 2009, the United States Pharmacopoeia heparin monograph—the testing standard applied to all heparin reaching the U.S. market—was revised to specify that nuclear magnetic resonance spectroscopy¹⁴ and

¹¹Takashi Kei Kishimoto et al., “Contaminated Heparin Associated with Adverse Clinical Events and Activation of the Contact System,” *New England Journal of Medicine*, vol. 358, no. 23 (June 5, 2008): 2457-2467 and Boyangzi Li et al., “Oversulfated Chondroitin Sulfate Interaction with Heparin-Binding Proteins: New Insights into Adverse Reactions from Contaminated Heparins,” *Biochemical Pharmacology*, vol. 78, no. 3 (August 2009): 292-300.

¹²Cafer Adiguzel et al., “Increased Prevalence of Antiheparin Platelet Factor 4 Antibodies in Patients May Be Due to Contaminated Heparin,” *Clinical and Applied Thrombosis/Hemostasis*, vol. 15, no. 2 (April 2009): 145-151.

¹³Andreas Greinacher and Theodore E. Warkentin, “Contaminated Heparin,” *New England Journal of Medicine*, vol. 359, no. 12 (September 18, 2008): 1291-1292.

¹⁴Nuclear magnetic resonance (NMR) spectroscopy measures the behavior of certain atomic nuclei, such as hydrogen nuclei, placed in a strong magnetic field. The molecular and chemical environment around the nuclei—that is, the chemical makeup and structure of a sample—produces characteristic shifts in the sample’s NMR spectrum.

chromatography¹⁵ be used both to positively identify heparin and to ensure the absence of OSCS in a sample.

During and after the contaminated heparin crisis, researchers investigated other methods to detect contaminated heparin. For example, FDA researchers have studied a screening method that is capable of detecting oversulfated contaminants like OSCS and could be used to test heparin-coated devices as well as heparin drug products.¹⁶ In addition, researchers have proposed that it might be possible to screen or check heparin using a blood test.¹⁷ Other researchers have investigated the use of more advanced approaches capable of detecting OSCS and other potential contaminants.¹⁸

¹⁵Chromatography is an analytical method based on separation of the components of a mixture by selective adsorption.

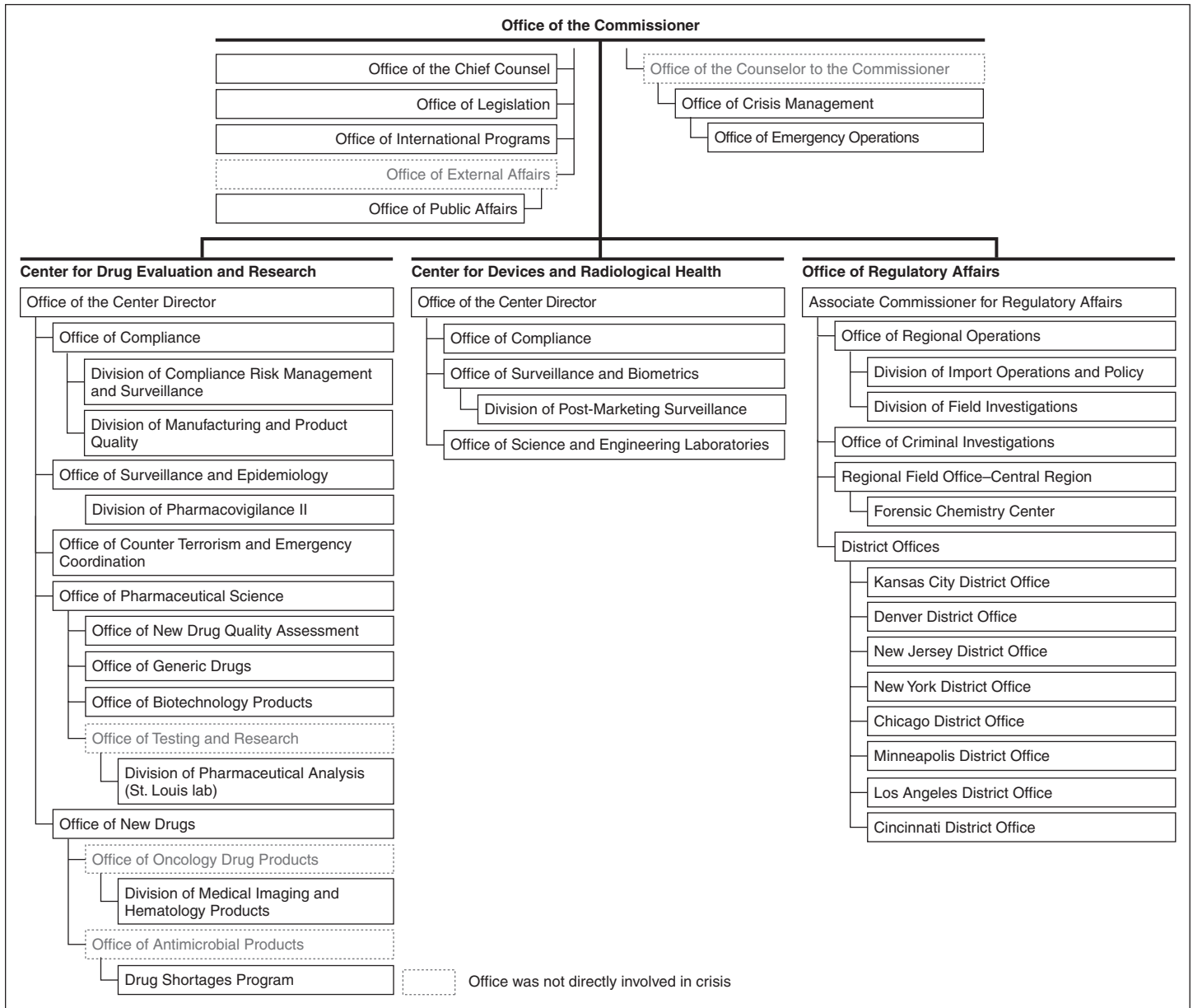
¹⁶Cecilia Tami et al., "Inhibition of Taq Polymerase as a Method for Screening Heparin for Oversulfated Contaminants," *Biomaterials*, vol. 29, no. 36 (2008): 4808-4814.

¹⁷Susanne Alban and Susanne Lühn, "Prothrombin Time for Detection of Contaminated Heparins," *New England Journal of Medicine*, vol. 359, no. 25 (December 18, 2008): 2732-2734.

¹⁸A number of research articles have been published in this area. For example, see Marco Guerrini et al., "The Tainted Heparin Story: An Update," *Thrombosis and Haemostasis*, vol. 102, no. 5 (November 2009): 907-911.

Appendix II: FDA Organizational Chart

FDA Centers and Offices Involved in the Heparin Crisis



Source: GAO analysis of FDA information.

Appendix III: FDA's Analyses of Adverse Events Associated with Heparin and Heparin-Containing Medical Devices

FDA reviewed its Adverse Event Reporting System (AERS) for adverse event reports associated with heparin drug products that the agency received from January 1, 2008, through March 31, 2008. FDA conducted two AERS analyses, including an analysis of allergic-type adverse events, including deaths, associated with heparin drug products, and an analysis of reports of deaths associated with heparin drug products that included allergic-type adverse events and reports that were not identified as allergic-type adverse events.

To identify reports for its AERS analysis of allergic-type adverse events, including deaths, associated with heparin drug products, FDA used an expanded case definition from the Centers for Disease Control and Prevention's (CDC) investigation of allergic-type events in hemodialysis patients. The CDC working case definition included confirmed and probable cases. A confirmed case, per the CDC case definition, was defined as an episode of anaphylactic or anaphylactoid reaction (severe hypersensitivity reactions) with angioedema (swelling) or urticaria (hives). A probable case was defined as an episode that included at least two of the following signs and symptoms: (1) generalized or localized sensations of warmth; (2) numbness or tingling of the extremities; (3) difficulty swallowing; (4) shortness of breath, wheezing, or chest tightness; (5) low blood pressure/tachycardia; or (6) nausea or vomiting.

Each report in FDA's AERS analyses of allergic-type adverse events also included at least one *Medical Dictionary for Regulatory Activities* (MedDRA) preferred term (PT) found under the Standardized MedDRA Query Plus (SMQ+) "anaphylactic reaction" as well as additional non-SMQ preferred terms of interest. MedDRA is clinically validated international medical terminology used by regulatory authorities (see table 1 for a list of FDA's search term criteria).

Appendix III: FDA's Analyses of Adverse Events Associated with Heparin and Heparin-Containing Medical Devices

Table 1: FDA's Standardized MedDRA Query Plus Search Term Criteria

Anaphylactic reaction SMQ+ and non-SMQ preferred terms	
Scope/category	Preferred term
SMQ narrow	Anaphylactic reaction, anaphylactic shock, anaphylactoid reaction, anaphylactoid shock, circulatory collapse, shock, type I hypersensitivity
SMQ Broad Oral/Respiratory PTs	Acute respiratory failure, asthma, bronchial oedema, bronchospasm, cardio-respiratory distress, chest discomfort, choking, choking sensation, cough, dyspnoea, hyperventilation, laryngeal dyspnoea, laryngeal oedema, laryngospasm, laryngotracheal oedema, oedema mouth, oropharyngeal spasm, oropharyngeal swelling, respiratory arrest, respiratory distress, respiratory failure, reversible airways obstruction, sensation of foreign body, sneezing, stridor, swollen tongue, throat tightness, tongue oedema, tracheal obstruction, tracheal oedema, wheezing
SMQ Broad Skin PTs	Allergic oedema, angioedema, erythema, eye oedema, eye swelling, eyelid oedema, face oedema, fixed eruption, flushing, generalised erythema, lip oedema, lip swelling, oedema, periorbital oedema, pruritus, pruritus allergic, pruritus generalised, rash, rash erythematous, rash generalised, rash pruritic, skin swelling, swelling, swelling face, urticaria, urticaria papular
SMQ Broad Cardiovascular PTs	Blood pressure decreased, blood pressure diastolic decreased, blood pressure systolic decreased, cardiac arrest, cardio-respiratory arrest, cardiovascular insufficiency, diastolic hypotension, hypotension
Non-SMQ PTs of interest	Diarrhoea, drug hypersensitivity, hyperhidrosis, hypersensitivity, loss of consciousness, nausea, vomiting

Source: FDA.

In addition, AERS cases meeting at least one of the following seven criteria were excluded from further analysis of allergic-types adverse events associated with heparin drug products:

1. cases judged to have a clearly identifiable alternative clinical explanation for the events,
2. cases in which the event reportedly occurred prior to the year 2007,
3. cases that could not be clinically interpreted,
4. cases of heparin-induced thrombocytopenia with or without thrombosis,
5. cases where it was uncertain if the patient was treated with heparin,
6. cases from literature reports that described unrelated issues, and
7. cases reported in error and retracted by the reporter.

In its analysis of AERS reports of deaths associated with heparin drug products, FDA included reports of both allergic-type adverse events as well as reports that were not identified as allergic-type adverse events since these cases had a fatal outcome. Table 2 shows the specific assessment criteria that FDA used in its analyses of AERS reports of deaths associated with heparin drug products to determine whether or not there was an association between the event of death and heparin. FDA did

Appendix III: FDA's Analyses of Adverse Events Associated with Heparin and Heparin-Containing Medical Devices

not apply these criteria to its analysis of allergic-types adverse events associated with heparin drug products. See figure 4 for details of FDA's AERS analyses.

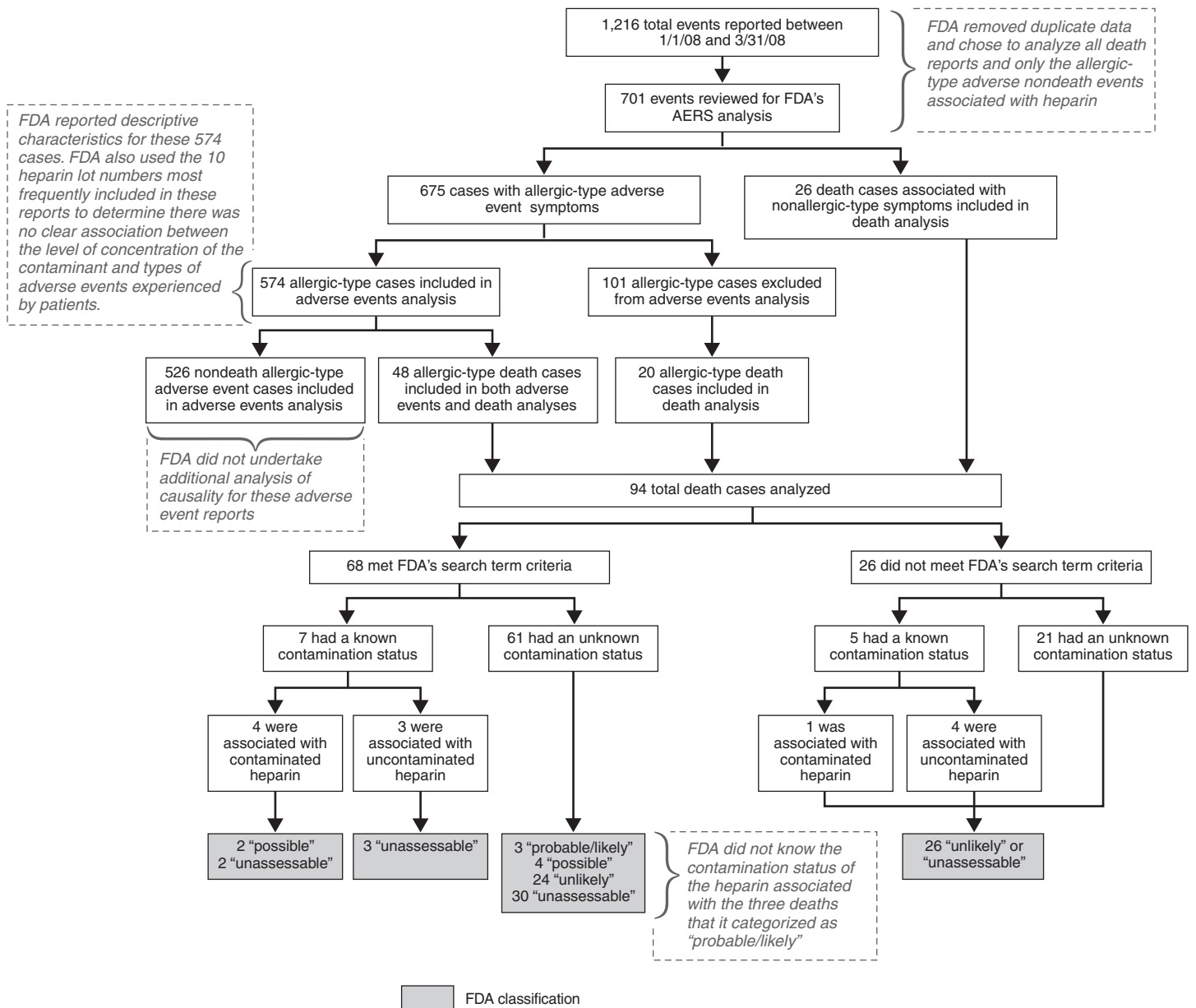
Table 2: FDA's AERS Death Analysis Assessment Criteria

Association	Assessment criteria
Probable/likely	Adverse event had reasonable time relationship to heparin administration (minutes to <= 1 hour), and Death unlikely related to disease or other drug products, and Death occurred during adverse event or within hours of heparin administration
Possible	Adverse event had reasonable time relationship to heparin administration (minutes to <= 1 hour), and Possible contributory role of disease or other drug products (i.e., another possible explanation for the event)
Unlikely	Event had an improbable time relationship (> 1 hour) to heparin administration, or Disease or other drug products provide plausible explanations (i.e., more likely explanation for the event than heparin administration)
Unable to assess	Cannot be assessed due to insufficient or contradictory information

Source: FDA.

Appendix III: FDA's Analyses of Adverse Events Associated with Heparin and Heparin-Containing Medical Devices

Figure 4: FDA Analysis of AERS Reports Associated with Heparin Drug Products

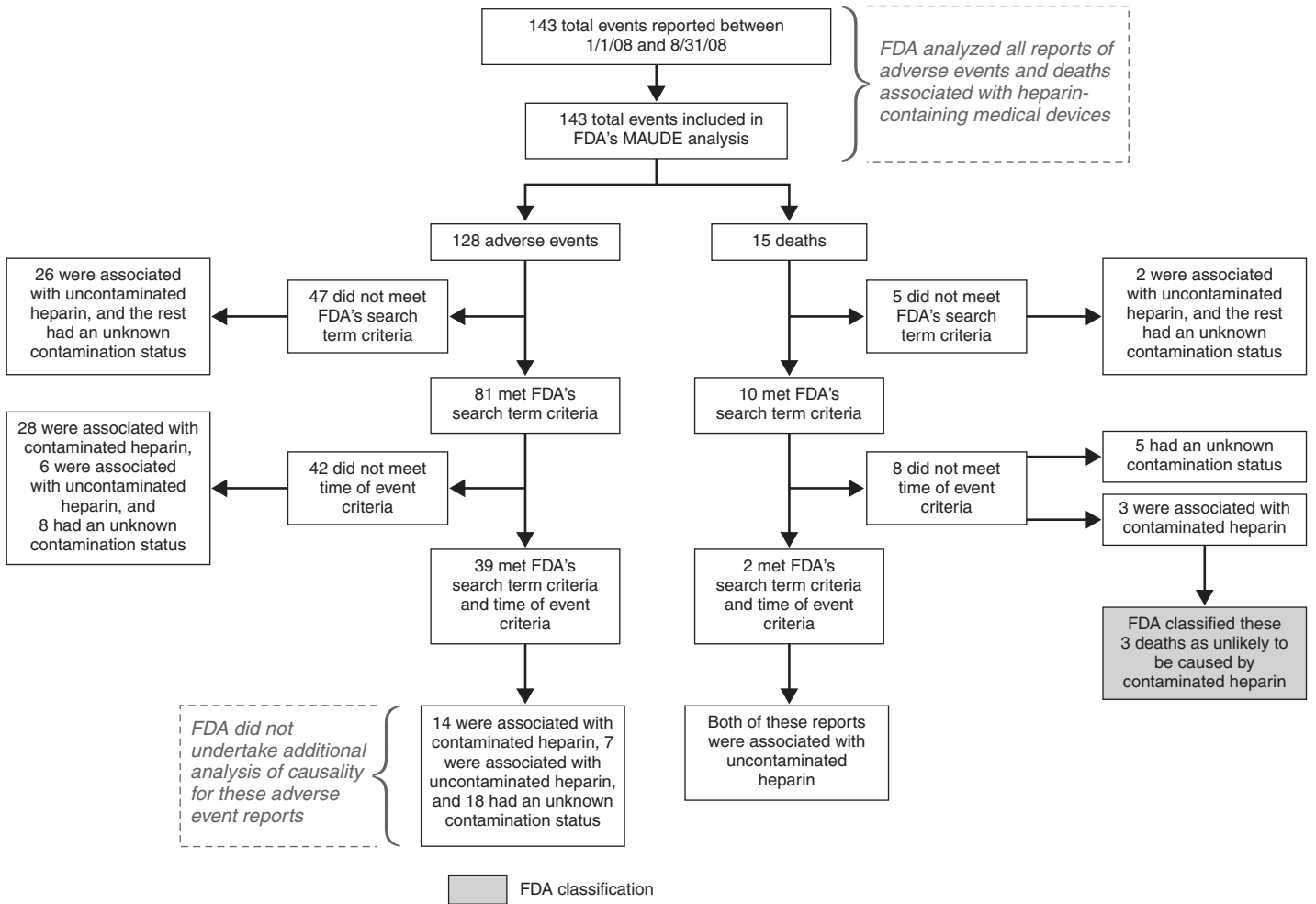


Source: GAO analysis of FDA data.

In its Manufacturer and User Facility Device Experience (MAUDE) analysis of adverse events, including deaths, associated with heparin-containing medical devices, FDA included all MAUDE reports that it received with an event date from January 1, 2008, through August 31, 2008. However, if a MAUDE report did not specifically have an event date listed, but was received by FDA during the specified time period, it was conservatively assumed to have occurred during that time frame and included in its MAUDE analysis. For each MAUDE report of death, FDA considered the patient's underlying condition, including the severity of the patient's condition, medications the patient was taking, and concomitant procedures or surgeries being undertaken to determine if there was a plausible explanation for the death. The presence of symptoms using the SMQ+ search terms as noted in table 1 were also taken into account as well as the timing of the event relative to the use of the heparin-containing medical device. In this analysis, FDA used assessment criteria similar to those in table 2 to classify the deaths associated with heparin-containing medical devices that were known to contain contaminated heparin as unlikely. FDA used a time criterion of 3 hours for the occurrence of the event for its MAUDE analysis compared with 1 hour for the AERS analyses because, according to an FDA official, adverse reactions to a heparin-containing medical device could potentially take longer to occur than when a patient receives a heparin drug product intravenously (see fig. 5 for details of FDA's MAUDE analysis).

Appendix III: FDA's Analyses of Adverse Events Associated with Heparin and Heparin-Containing Medical Devices

Figure 5: FDA Analysis of MAUDE Reports Associated with Heparin-Containing Medical Devices



Appendix IV: Comments from the Department of Health and Human Services



DEPARTMENT OF HEALTH & HUMAN SERVICES

OFFICE OF THE SECRETARY

Assistant Secretary for Legislation
Washington, DC 20201

OCT 15 2010

Marcia Crosse
Director, Health Care
U.S. Government Accountability Office
441 G Street N.W.
Washington, DC 20548

Dear Ms. Crosse:

Attached are comments on the U.S. Government Accountability Office's (GAO) correspondence entitled: "FOOD AND DRUG ADMINISTRATION: Response to Heparin Contamination Helped Protect Public Health but More Controls are Needed for Working with External Entities" (GAO 11-95).

The Department appreciates the opportunity to review this correspondence before its publication.

Sincerely,

A handwritten signature in cursive script that reads "Jim R. Esquea".

Jim R. Esquea
Assistant Secretary for Legislation

Attachment

GENERAL COMMENTS OF THE DEPARTMENT OF HEALTH AND HUMAN SERVICES (HHS) TO THE GOVERNMENT ACCOUNTABILITY OFFICE'S DRAFT REPORT ENTITLED, "FOOD AND DRUG ADMINISTRATION: RESPONSE TO HEPARIN CONTAMINATION HELPED PROTECT PUBLIC HEALTH BUT MORE CONTROLS ARE NEEDED FOR WORKING WITH EXTERNAL ENTITIES" (GAO-11-95)

The Department appreciates the opportunity to review and comment on this draft report.

For the Food and Drug Administration (FDA), the heparin story began in January 2008, when the agency was confronted with an escalating public health emergency in which clusters of dialysis patients were experiencing severe allergic reactions during treatment. Although the initial cause of the reactions was unknown, a common link was the use of the blood thinner, heparin, a medically necessary drug. The complicating factor was that the available screening methods were not able to detect the contaminant or contaminants causing the problems. Because of this undetectable adulterant, FDA was not able to distinguish good lots of heparin from bad lots. Agency officials could not withdraw all heparin from the market to avoid the risk of contaminated heparin because a complete market withdrawal would have caused the shortage of a drug that is necessary for the safe, daily treatment of hundreds of thousands of American patients.

To minimize the risk to patients of both contaminated heparin and a shortage of heparin, the agency mounted an immediate effort to identify the contaminant that was causing the adverse reactions.

By the end of February 2008, FDA scientists had developed new qualitative methods that helped distinguish good from bad heparin lots. These qualitative screening methods were essential to the agency's initial efforts to implement a step-wise process for recalling the lots of heparin most likely to be contaminated. However, these tests were not sufficient to safeguard the heparin supply and reduce risks to patients because they were imprecise, likely classified some good heparin lots as suspect, and were not capable of identifying and quantifying the contaminant, oversulfated chondroitin sulfate (OSCS), and establishing OSCS's linkage to the observed adverse events. Removal of all suspect batches from the U.S. market, including some good heparin (non-contaminated) lots, could have created a heparin shortage that would have severely harmed patients. To avoid this harm, it was critically important to single out the adulterant that was actually causing the adverse events and to establish—through a robust method of scientific validation—the biological link between the suspected culprit, OSCS, and the adverse events.

To accomplish this task, FDA needed to quickly identify and enlist the help of the world's leading experts in the field of the molecular characterization of heparin, a complex polysaccharide.

Two peer reviewed scientific articles (*Nature Biotechnology*¹ and *New England Journal of Medicine*²) were published to describe these validation methods and to communicate the findings

¹ Nature Biotechnology, Oversulfated Chondroitin Sulfate is a Contaminant in Heparin Associated with Adverse Clinical Events, April 23, 2008.

GENERAL COMMENTS OF THE DEPARTMENT OF HEALTH AND HUMAN SERVICES (HHS) TO THE GOVERNMENT ACCOUNTABILITY OFFICE'S DRAFT REPORT ENTITLED, "FOOD AND DRUG ADMINISTRATION: RESPONSE TO HEPARIN CONTAMINATION HELPED PROTECT PUBLIC HEALTH BUT MORE CONTROLS ARE NEEDED FOR WORKING WITH EXTERNAL ENTITIES" (GAO-11-95)

to the global scientific and regulatory communities. The *New England Journal of Medicine* article in particular documents the painstaking process of scientific validation that these experts and FDA scientists pursued to link definitively OSCS to the adverse reactions. This process included, among other things, nuclear magnetic resonance imaging, chemical testing, and animal studies to replicate the allergic response experienced by the patients who suffered ill effects.

Because of this work, higher standards are now applied to a drug that continues to be essential for patients every day, in this country and throughout the world. In addition, the scientific work establishing the biological link between OSCS and the allergic reactions has given companies throughout the world the ability to screen for it in their supplies of crude heparin, the component from which they make the finished product. Today, this testing of crude heparin supplies is central to current regulatory efforts to safeguard the global supply of heparin.

This successful effort to protect public health would not have been possible without the unique expertise and extraordinary efforts of the outside scientists with whom FDA engaged.

The heparin story, however, is bigger than a crisis that threatened the health and lives of people around the world. It is a story of the increasing globalization of the supply chains of medically necessary drugs, medical devices, and other products. It is a story of the increasing opportunities those extended and fractured supply chains present to those who, for economic gain or to intentionally harm people, are willing to adulterate foods and drugs. It is a story of how FDA, working within the constraints it faces in both capacity and authority, has worked diligently to prevent such assaults on the public health. It is not the first such story, and it may not be the last. It is a clarion call to the agency, and anyone with an interest in promoting the public health, to improve the assays for testing drug and other products' ingredients, to improve controls on quality in, and to collect better information about, the supply chains of products, and to develop tools for anticipating, preventing, and prosecuting such crimes and acts of terrorism.

Since the heparin contamination crisis, FDA has taken a number of significant steps to safeguard the U.S. supply of this medically necessary drug. The agency has increased inspections of heparin manufacturing and testing facilities related to the U.S. heparin supply. The U.S. Pharmacopoeia standard now requires all heparin manufacturers to test for the presence of OSCS. The agency has adopted a risk-model designed to identify other drugs that may be at increased risk for economically motivated adulteration. It has improved the databases that it maintains with information about drug supply chains. It has enhanced its efforts to work with and build the capacity of other regulators across the globe.

The Congress also has begun work that affects these efforts. New legislation currently is under consideration by Congress that would provide the agency helpful tools to further secure our

² The *New England Journal of Medicine*, Contaminated Heparin Associated with Adverse Clinical Events and Activation of the Contact System, June 5, 2008. This article (10.1056/NEJMoa0803200) was published at www.nejm.org on April 23, 2008.

GENERAL COMMENTS OF THE DEPARTMENT OF HEALTH AND HUMAN SERVICES (HHS) TO THE GOVERNMENT ACCOUNTABILITY OFFICE'S DRAFT REPORT ENTITLED, "FOOD AND DRUG ADMINISTRATION: RESPONSE TO HEPARIN CONTAMINATION HELPED PROTECT PUBLIC HEALTH BUT MORE CONTROLS ARE NEEDED FOR WORKING WITH EXTERNAL ENTITIES" (GAO-11-95)

nation's drug supply chain and ensure that the agency can hold industry accountable for the security and integrity of their supply chains and the quality control systems they use to produce drugs for the American people. In particular, the bill provides for the following new authorities:

- Drug supply quality and safety – to require foreign and domestic drug manufacturers to implement quality systems and adopt plans to identify and mitigate hazards.
- Documentation for imports – to provide FDA with explicit authority to refuse admission of drugs to the United States if all required information about the import is not submitted to FDA.
- Subpoena authority – to grant FDA authority to issue subpoenas to compel production of documents and witnesses related to possible violations.
- Prohibition against delaying, limiting or refusing inspection – to grant FDA explicit authority to refuse admission of drugs to the United States if inspection is delayed, limited or refused.
- Criminal and civil penalties – to modernize penalties for criminal violations of the Federal Food, Drug, and Cosmetic Act to include higher maximum prison sentences; and to grant authority to impose civil money penalties for violations relating to drugs and improper import entry filings.
- Administrative detention and destruction – to grant FDA the authority to administratively detain violative drug products, an authority the agency already has for food and devices; and to streamline the process for the destruction of drugs offered for import that are valued at \$2,000 or less or that pose a reasonable probability of causing a significant adverse health effect.
- Extraterritorial jurisdiction – to provide FDA with explicit legal authority to pursue prosecutions for conduct that occurs outside of the United States.

FDA has learned from the heparin crisis to improve its processes for responding to emergencies. For example, the agency has recently updated its Emergency Operations Plan, and it has also implemented a policy to address risks in using outside experts who provide services gratuitously in such emergencies, a policy that is responsive to GAO's single recommendation in the report. The policy provides that in an emergency, FDA will consider and obtain, as appropriate, external scientific experts as the agency responds to, and resolves, the crisis. It will obtain these resources expeditiously, while giving due consideration to risks that may be presented in collaborative arrangements with external entities, including conflicts of interest. Responsible FDA staff will consult internally with the appropriate FDA offices as the agency addresses such risks and will document its decisions about such issues. The agency will also disclose information about its use of external experts and any relevant conflicts of interest.

Appendix V: GAO Contact and Staff Acknowledgments

GAO Contact

Marcia Crosse, (202) 512-7114 or crosssem@gao.gov

Acknowledgments

In addition to the contact named above, key contributors to this report were Tom Conahan, Assistant Director; Susannah Bloch; Helen Desaulniers; Linda Galib; Julian Klazkin; Lisa A. Lusk; and Samantha Poppe.

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