

September 2009

OVERSIGHT OF CLINICAL INVESTIGATORS

Action Needed to Improve Timeliness and Enhance Scope of FDA's Debarment and Disqualification Processes for Medical Product Investigators

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Highlights of [GAO-09-807](#), a report to congressional requesters

Why GAO Did This Study

The Food and Drug Administration (FDA) oversees the clinical investigators who conduct research involving new drugs, biologics, and medical devices to ensure that their conduct does not compromise the safety of clinical trial participants or the integrity of clinical trial data. FDA can debar or disqualify investigators who have engaged in misconduct such as submitting fraudulent data. Debarred or disqualified investigators cannot engage in certain activities related to clinical research. GAO was asked to review FDA's debarment and disqualification processes. GAO examined the length of time debarment and disqualification processes have taken and factors for those time frames, and the statutory and regulatory limitations of debarment and disqualification. GAO reviewed laws, regulations, and FDA files through November 5, 2008, for (1) all investigators, study coordinators, and sub-investigators for whom FDA pursued debarment since receiving debarment authority in 1992; and (2) all clinical investigators for whom FDA pursued disqualification since FDA adopted its current process for initiating proceedings in 1998.

What GAO Recommends

To improve its oversight, the Commissioner of FDA should pursue extending FDA's debarment authority; extend disqualification to include drugs, biologics, and medical devices; and ensure the timely completion of debarment and disqualification proceedings. FDA agreed with GAO's recommendations.

[View GAO-09-807](#) or [key components](#). For more information, contact Marcia Crosse at (202) 512-7114 or crossem@gao.gov.

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What GAO Found

More than half of the debarment proceedings in GAO's review took 4 or more years, and factors contributing to these time frames included internal control weaknesses in the debarment process and competing priorities among responsible staff. FDA has statutory authority to debar individuals who have been convicted of felonies or certain misdemeanors related to the development, approval, or regulation of a drug or biologic. For the 18 proceedings GAO reviewed, the length of time from an individual's conviction through debarment (or as of November 5, 2008, for pending proceedings) ranged from about 1 year to nearly 11 years. Factors that contributed to delays included that FDA staff faced competing priorities and FDA had not established internal controls, such as time frames for the completion of steps in the debarment process. FDA has made or planned changes that could improve timeliness (e.g., by establishing time frames in March 2009), but the effects of such actions have yet to be seen.

The time taken for disqualification proceedings varied and proceedings took longer when the investigator contested disqualification. FDA may disqualify investigators who repeatedly or deliberately failed to comply with FDA regulations or submitted false information to FDA or the sponsor of a clinical trial. For the 52 disqualification proceedings GAO reviewed, the length of time from initiation of a disqualification proceeding to its conclusion (or as of November 5, 2008, for pending proceedings) ranged from 26 days to more than a decade, with about one-third taking more than 2 years. In general, the more steps taken by the investigator to contest disqualification, the longer it took to complete the proceeding. Disqualification proceedings initiated in 1998 through 2001 generally took longer than proceedings that were initiated more recently. FDA officials told us that a lack of time frames for these proceedings—an internal control weakness—may have contributed to longer proceedings. FDA made changes to its disqualification process (e.g., by establishing time frames in June 2008 and January 2009) that could further improve timeliness, but the full effect of these changes remains to be seen.

FDA's debarment authority does not fully extend to involvement with medical devices, and its regulations do not extend disqualification for drugs and biologics to medical devices and vice versa. As a result, an individual may be debarred from involvement with drugs and biologics, but not from involvement with medical devices, regardless of the kind of misconduct in which the individual engaged. FDA's disqualification regulations allow an investigator who is disqualified for conduct related to drugs or biologics to serve as an investigator for medical devices; likewise, an individual who FDA disqualified for conduct related to medical devices remains able to serve as a clinical investigator for drugs and biologics.

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Abbreviations

CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
FDA	Food and Drug Administration
NIDPOE	Notice of Initiation of Disqualification Proceedings and Opportunity to Explain
NOOH	Notice of Opportunity for Hearing

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United States Government Accountability Office
Washington, DC 20548

September 25, 2009

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

The Honorable Greg Walden
Ranking Member
Subcommittee on Oversight and Investigations
Committee on Energy and Commerce
House of Representatives

The Food and Drug Administration (FDA) has oversight responsibilities for clinical investigators who conduct research involving investigational medical products—including drugs, biologics, and devices¹—to ensure that their conduct does not compromise the quality or integrity of clinical trial data or the safety of clinical trial participants. The quality or integrity of the clinical trial data that FDA uses to determine whether an investigational medical product is safe and effective for the U.S. market can be compromised by misconduct, such as falsification of these results, and the safety of clinical trial participants can be jeopardized by misconduct, such as failing to obtain their informed consent. For example, if a clinical investigator falsifies data or fails to report trial participants' adverse reactions to an investigational drug, flawed data could be used to assert the drug's safety and the drug could potentially endanger the health of those who take it. Timely action against individuals who engage in such misconduct is a key component of effective oversight.

As part of its oversight activities, FDA can take actions against clinical investigators who have engaged in certain types of misconduct; debarment and disqualification are two such actions. FDA has express statutory authority to debar individuals—including clinical investigators and the

¹Investigational medical products include drugs, biologics, or devices that are the object of clinical investigations. For the purposes of this report, drugs refer to human drugs. Biologics include blood, vaccines, allergenic products, certain tissues, and cellular and gene therapies. Devices include medical devices used for the diagnosis, cure, mitigation, treatment, or prevention of a disease. In addition to drugs, biologics, and devices, FDA regulates other products, including animal drugs, food additives, and cosmetics, and was recently authorized to regulate tobacco products.

sub-investigators and study coordinators who work for them²—who have been convicted of certain crimes or who have engaged in certain misconduct related to the development or approval of any drug or biologic.³ For example, FDA can debar an individual convicted of a felony in connection with submitting fraudulent data for nonexistent clinical trial participants or falsifying a report to conceal a failure to conduct a clinical trial as required. Debarred individuals cannot provide services to the drug or biologic industry as a clinical investigator, sub-investigator, study coordinator, or in any other capacity. Under FDA’s regulations, the agency may disqualify clinical investigators who repeatedly or deliberately failed to comply with FDA regulations or who repeatedly or deliberately submitted false information to FDA or the sponsor of the clinical trial in a required report. For example, FDA can disqualify a clinical investigator who failed to obtain informed consent from clinical trial participants. Disqualified clinical investigators are prohibited from receiving one or more types of investigational medical products, which include drugs, biologics, and devices, and as a result, they are prevented from serving as clinical investigators for clinical trials of these products. FDA posts on its Web site lists of those individuals whom the agency has debarred or disqualified. Sponsors of applications for new drugs and biologics must certify that debarred individuals did not provide services to them, and sponsors of investigational medical products may not provide these products to investigators who have been disqualified to receive them.

Reports of some delays in debarring or disqualifying clinical investigators and questions about the scope of FDA’s debarment and disqualification activities have focused attention on FDA’s oversight of clinical investigators.⁴ Previous reports have noted weaknesses in other aspects of FDA’s oversight of clinical investigators. We previously reported that FDA’s oversight efforts may allow violations of protections to clinical trial

²Clinical investigators have responsibility for the conduct of a particular clinical trial at one or more locations. Sub-investigators and study coordinators work under the supervision of clinical investigators and provide services such as recruiting and collecting data from clinical trial participants.

³21 U.S.C. § 335a. Debarment is also possible for certain criminal convictions unrelated to the development or approval of a drug or biologic. The drugs and biologics referred to in the statute are included in the definition of “drug product.” 21 U.S.C. § 321(dd).

⁴See, for example, U.S. House of Representatives, Committee on Energy and Commerce, Minority Staff, *FDA’s Faulty Safeguards Against Corruption: Concerns Over Debarment Use and Authority*. Prepared for Ranking Member Joe Barton (Washington, D.C.: Feb. 2008).

participants to go undetected because FDA inspected only a small percentage of the sites where clinical trials were conducted and FDA typically carried out these inspections after clinical trials were concluded.⁵ The Department of Health and Human Services's Office of Inspector General previously reported on weaknesses in FDA's oversight of clinical trials, including a lack of clear, specific guidance and inconsistency across FDA components in their responses to inspectional findings.⁶ You asked us to review factors contributing to delays in FDA's debarment and disqualification proceedings. This report discusses (1) the length of time FDA's debarment proceedings have taken and the factors contributing to the length of time they have taken, (2) the length of time FDA's disqualification proceedings have taken and the factors contributing to the length of time they have taken, and (3) statutory and regulatory limitations to debarment and disqualification.

To determine how long FDA's debarment proceedings have taken and to identify factors that contributed to the length of time they have taken, we reviewed FDA's files regarding all clinical investigators, sub-investigators, and study coordinators whom FDA pursued or considered pursuing for debarment from the time that it was given authority to do so on May 13, 1992, through September 9, 2008.⁷ To identify these individuals, we reviewed information about FDA's debarment proceedings from *Federal Register* notices (including proposal to debar letters, which FDA uses to initiate debarment actions, and debarment orders, which FDA uses to

⁵See, for example, GAO, *Scientific Research: Continued Vigilance Critical to Protecting Human Subjects*, [GAO/HEHS-96-72](#) (Washington, D.C.: Mar. 8, 1996); GAO, *Human Subjects Research: HHS Takes Steps to Strengthen Protections, But Concerns Remain*, [GAO-01-775T](#) (Washington, D.C.: May 23, 2001); and GAO, *Human Subjects Research: Undercover Tests Show the Institutional Review Board System Is Vulnerable to Unethical Manipulation*, [GAO-09-448T](#) (Washington, DC.: Mar. 26, 2009).

⁶See, for example, two reports by the Department of Health and Human Services's Office of Inspector General: *FDA Oversight of Clinical Investigators*, OEI-05-99-00350 (Washington, D.C.: Department of Health and Human Services, June 2000); and *The Food and Drug Administration's Oversight of Clinical Trials*, OEI-01-06-00160 (Washington, D.C.: Department of Health and Human Services, Sept. 2007).

⁷We included sub-investigators and study coordinators because, like clinical investigators, they interacted directly with clinical trial participants. Clinical investigators, sub-investigators, and study coordinators are a subset of individuals who are subject to debarment. We excluded individuals who worked in other roles and who were debarred, for example, we excluded a senior vice president and a chemist whose misconduct could have affected the information available to FDA when evaluating applications to market new drugs or biologics, but who generally did not interact directly with clinical trial participants.

complete debarment actions) and FDA's Web site, and obtained additional information from FDA about individuals whom FDA pursued or considered pursuing for debarment. We identified 18 proceedings—13 involving clinical investigators and 5 involving study coordinators.⁸ For each proceeding, we reviewed relevant files in the FDA center that initiated the debarment action—either the Center for Drug Evaluation and Research (CDER) for misconduct related to drugs or the Center for Biologics Evaluation and Research (CBER) for misconduct related to biologics—and in FDA's Division of Dockets Management, which maintains publicly available information about debarment proceedings. To determine the length of time each completed debarment proceeding took, we calculated the number of calendar days from the date of the individual's conviction (or, if the individual's conviction occurred before FDA received debarment authority, from the date when FDA received debarment authority—May 13, 1992) through publication of the debarment order in the *Federal Register*.⁹ For debarment proceedings that were pending at the time of our file review, we calculated the number of calendar days through the last day of our file review (Nov. 5, 2008).¹⁰ To identify factors that contributed to the length of time FDA's debarment proceedings have taken, we analyzed the information we obtained from FDA's files and obtained additional information from FDA officials (for example, by asking what occurred during long intervals for which we saw no documented activity). We examined laws, regulations, and guidance to determine whether there were criteria relevant to the times taken by debarment proceedings. We also examined internal control standards, which include the need to establish policies and procedures to help ensure

⁸One of the study coordinators was also a sub-investigator.

⁹For completed proceedings, we used the date that the debarment order was published in the *Federal Register* as the date of completion of the debarment proceeding. For the completed proceedings we reviewed, this date was also the effective date of the debarment order.

¹⁰We defined a debarment proceeding as pending if, as of the last date of our file review (Nov. 5, 2008), FDA had issued a proposal to debar letter, but had not completed the debarment proceeding, or if FDA had identified an individual as one whose conviction could serve as a basis for debarment, but for whom FDA had not yet issued a proposal to debar letter.

effective and efficient operations.¹¹ We also interviewed FDA officials, including those involved with FDA's Debarment Working Group, which was formed by FDA to review FDA's debarment process, including the length of debarment proceedings.

To determine how long FDA's disqualification proceedings have taken and identify factors that contributed to the length of time they have taken, we reviewed FDA's files regarding all clinical investigators for whom FDA pursued disqualification by issuing a Notice of Initiation of Disqualification Proceedings and Opportunity to Explain (NIDPOE) letter from January 1, 1998, through September 9, 2008, for conduct related to drugs, biologics, or devices, whether these clinical investigators were ultimately disqualified or not.¹² To identify these individuals, we reviewed information about FDA's disqualification proceedings from FDA's Web site and obtained additional information from FDA about individuals for whom FDA pursued disqualification. We identified 52 proceedings. For each proceeding, we reviewed relevant files in the FDA center that initiated the disqualification proceeding—CDER for drugs, CBER for biologics, or the Center for Devices and Radiological Health (CDRH) for devices—as well as in other FDA offices that maintained files relating to these disqualification proceedings. These other offices included the Office of Enforcement, the Office of the Ombudsman, and the Good Clinical Practice Program, an office within FDA responsible for coordinating policies for the conduct of clinical trials of FDA-regulated products that involve human participants.¹³ To determine the length of time each completed disqualification proceeding took, we calculated the number of calendar days from the date of issuance of the NIDPOE letter through the completion of the disqualification proceeding. For disqualification

¹¹These standards provide an overall framework for establishing and maintaining internal control and for identifying and addressing major performance and management challenges and areas at greatest risk of fraud, waste, abuse, and mismanagement. For example, under the standards for internal control, information should be recorded and communicated to management and others within an entity who need it and within a time frame that enables them to carry out their internal control and other responsibilities. See GAO, *Standards for Internal Control in the Federal Government*, [GAO/AIMD-00-21.3.1](#) (Washington, D.C.: Nov. 1999) and its supplemental guide, *Internal Control Management and Evaluation Tool*, [GAO-01-1008G](#) (Washington, D.C.: Aug. 2001).

¹²According to FDA officials, prior to 1998, the agency typically initiated disqualification proceedings without issuing a NIDPOE letter.

¹³In August 2009, the Good Clinical Practice Program was renamed the Office of Good Clinical Practice.

proceedings that were pending at the time of our file review, we calculated the number of calendar days through the last day of our file review (Nov. 5, 2008). To identify factors that contributed to the length of time FDA’s disqualification proceedings have taken, we analyzed the information we obtained from FDA’s files and obtained additional information from FDA officials (for example, by asking what occurred during long intervals for which we saw no documented activity). To determine whether the length of time taken for disqualification proceedings changed during the years covered in our review, we divided disqualification proceedings into three groups based on the date that FDA issued the NIDPOE letter—those initiated before 2002, those initiated in 2002 through 2005, and those initiated after 2005. We examined laws, regulations, guidance, and standards for internal control to determine whether there were criteria relevant to the times taken by disqualification proceedings. We also interviewed FDA officials, including those in each of the offices in which we reviewed disqualification files.

To identify statutory and regulatory limitations to debarment and disqualification, we reviewed relevant laws, regulations, and guidance; reviewed files documenting FDA’s debarment and disqualification proceedings; and interviewed FDA officials involved with debarment and disqualification. We conducted this performance audit from June 2008 to September 2009, 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. For additional information about our scope and methodology, see appendix I.

Background

FDA has responsibilities for overseeing clinical investigators who conduct clinical trials of investigational medical products, including drugs, biologics, and devices. As part of its oversight activities, FDA can take actions such as debarment or disqualification against investigators and other individuals who have engaged in certain types of misconduct.

FDA’s Oversight of Clinical Investigators

FDA oversees clinical investigators to ensure that they comply with federal regulations governing the conduct of clinical trials. These regulations, which are intended to protect the quality and integrity of the clinical trial data and the safety of clinical trial participants, include requirements for the following:

-
- Obtaining informed consent from clinical trial participants,
 - Obtaining approval for conducting a clinical trial from an institutional review board that has been tasked with reviewing that trial's protections for participants,¹⁴
 - Following the research plan for the clinical trial (including a protocol) that was approved by the institutional review board,
 - Reporting adverse events associated with the clinical trial, and
 - Submitting reports.

FDA can disqualify clinical investigators who repeatedly or deliberately violate applicable regulations or who repeatedly or deliberately submit false information in a required report, and in some cases, an individual's misconduct may result in a criminal conviction, providing a basis for debarment. FDA's debarment and disqualification proceedings each consist of a series of steps involving actions taken by FDA and by the affected individual. These steps provide the individual with an opportunity to contest the charges against him or her. The number of steps involved for each proceeding can vary depending, for example, on whether the individual chooses to contest the charges by providing information or arguments against debarment or disqualification.

Debarment

Under the Generic Drug Enforcement Act of 1992,¹⁵ FDA has authority to debar individuals—including clinical investigators, sub-investigators, and study coordinators—who have been convicted of certain crimes, or engaged in other misconduct, related to the development, approval, or regulation of any drug or biologic from involvement with drugs and biologics.¹⁶ (FDA does not have comparable authority with regard to an individual involved in the medical device industry.) There are two types of

¹⁴An institutional review board is an entity formally designated to review clinical trials and other research involving human subjects, with the purpose of protecting the rights and welfare of the clinical trial subjects. See 21 C.F.R. § 56.102(g) (2009).

¹⁵Pub. L. No.102-282, § 2, 106 Stat. 149-158 (1992) (codified at 21 U.S.C. § 335a).

¹⁶A debarred individual is prohibited from providing any service to—that is, from involvement with—any entity (an individual, partnership, association, or corporation) that has an approved or pending drug or biologic application. 21 U.S.C. §§ 321(e), 335a(c)(1)(B).

debarment, and if based on a criminal conviction, debarment must be initiated within 5 years of the date of conviction:

- **Mandatory.** Debarment is mandatory—and permanent—when FDA finds that an individual has been convicted of a felony under federal law for misconduct relating to the development or approval of any drug or biologic, or otherwise relating to the regulation of any drug or biologic.¹⁷
- **Permissive.** FDA may, but is not required to, seek permissive debarment—which is not permanent—under certain other conditions, for example, if the individual was convicted of a felony under state law for conduct related to the development or approval of any drug or biologic.¹⁸ For permissive debarment, FDA must determine that debarment is appropriate and determine the period of debarment by considering factors such as the nature and seriousness of the offense or offenses involved. An individual may be permissively debarred for up to 5 years for each offense. If the individual is permissively debarred for multiple offenses, the Commissioner of FDA may determine whether debarment periods will run concurrently or consecutively.¹⁹

As shown in figure 1, FDA’s debarment process involves multiple possible steps. The process starts when FDA learns of an individual’s conviction, determines that it provides a basis for debarment, and drafts a proposal to debar letter. For the debarment proceedings we reviewed, the relevant FDA center (CDER for drugs or CBER for biologics) was responsible for determining if there was a basis for debarment and drafting the proposal to debar letter, with input from the Office of the Chief Counsel.²⁰ FDA provides the individual with a notice of its proposal to debar and provides

¹⁷21 U.S.C. §§ 321(dd); 335a(a)(2), (c)(2)(A)(ii).

¹⁸21 U.S.C. § 335a(b)(2)(B)(i)(I), (c)(2)(A)(iii). FDA may also permissively debar an individual who has not been convicted of a crime or convicted of a crime unrelated to the development or approval of a drug or biologic. For example, FDA may permissively debar an individual if the individual materially participated in acts that were the basis for another individual’s conviction for certain crimes, such as a felony conviction under state law for conduct related to the development or approval of a drug or biologic. In such cases, FDA must also find that the individual’s behavior demonstrates a pattern of conduct suggesting that the individual may violate other requirements under the Federal Food, Drug, and Cosmetic Act relating to drugs or biologics. 21 U.S.C. § 335a(b)(2)(B)(iii).

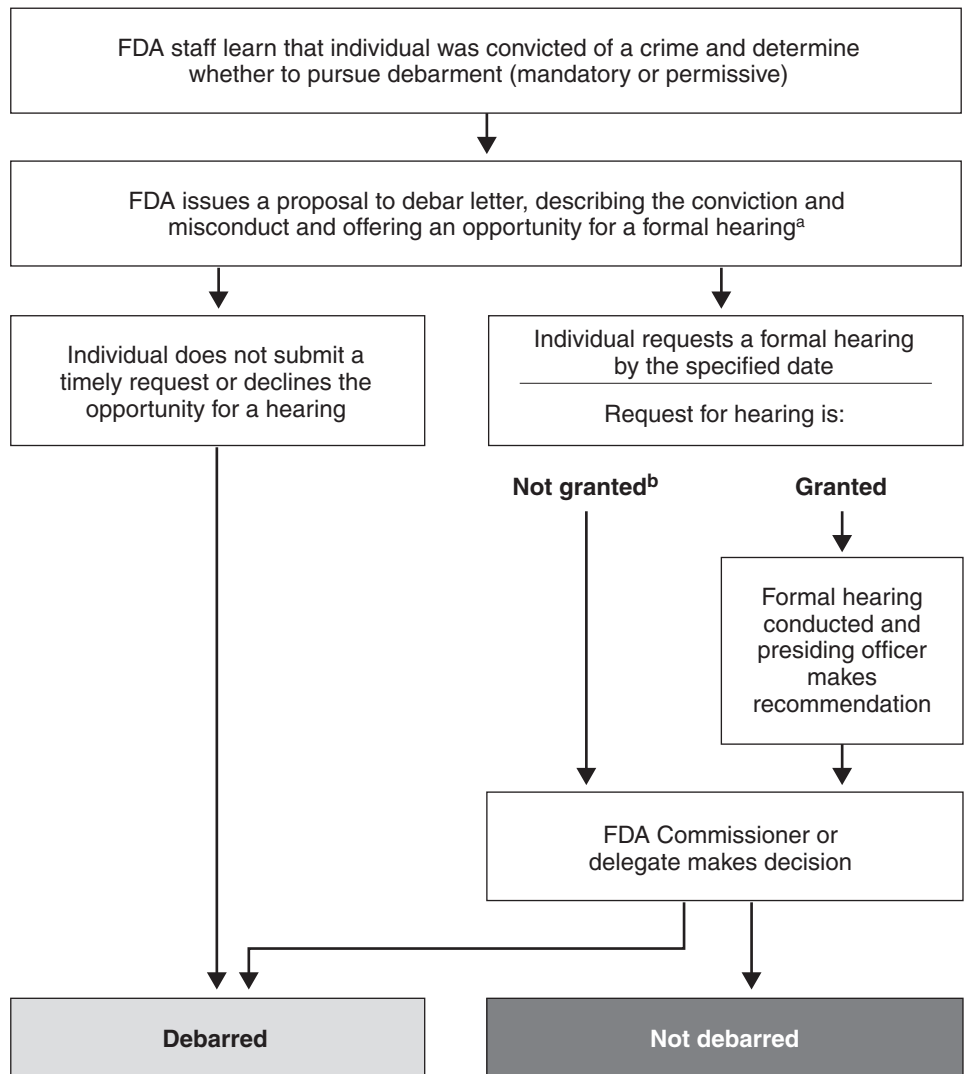
¹⁹21 U.S.C. § 335a(c)(2)(A), (c)(3).

²⁰As of March 2009, the Office of Enforcement—not the center—is responsible for determining whether to pursue debarment and drafting the proposal to debar letter.

an opportunity for a formal hearing to demonstrate why he or she should not be debarred.²¹ If the individual requests a hearing, he or she must provide information on disputed issues of material fact to justify a hearing, such as whether the individual was actually convicted as alleged in the notice and, if so, whether this conviction provides a basis for debarment. FDA evaluates this information and determines whether to grant a hearing. If the FDA Commissioner determines that there is no substantial issue of material fact, then he or she denies the hearing and debars the individual by issuing an order of debarment. FDA publishes a debarment order in the *Federal Register*.

²¹Formal hearings conducted in the course of debarment proceedings are conducted under part 12, Title 21, Code of Federal Regulations, 2009.

Figure 1: FDA's Debarment Process for Individuals



Source: GAO.

Notes: This figure presents the major steps that could be involved in the debarment proceedings we reviewed. These proceedings involved clinical investigators, sub-investigators, and study coordinators for whom FDA pursued or considered pursuing debarment from May 13, 1992, through September 9, 2008. The number of steps involved for a proceeding can vary depending, for example, on whether the individual chooses to contest the charges by requesting a hearing. All clinical investigators, sub-investigators, and study coordinators whom FDA pursued or considered pursuing for debarment as of the last date of our file review (November 5, 2008) had been convicted of a crime.

^aProposal to debar letters specify that if the individual chooses to respond, he or she must submit a written notice of request for a formal hearing within 30 days of receiving the letter and must submit information on which the individual relies to justify a hearing within 60 days of receiving the letter.

²¹When a request for a hearing is denied, the FDA Commissioner (or delegate) generally issues a decision that includes both a denial of the hearing and a debarment order.

Debarred individuals are prohibited from involvement with drugs and biologics. Debarment does not preclude such individuals from serving in any capacity to an entity that intends to market or is marketing a medical device or other FDA-regulated product, such as food additives or cosmetics.

An individual's debarment can end when the individual's permissive debarment period has ended or if FDA terminates the individual's debarment. FDA may terminate debarment if, for example, the conviction that served as the basis for the individual's debarment is reversed.²²

Disqualification

Under federal regulations, FDA may disqualify clinical investigators from receiving investigational drugs, biologics, or devices if they repeatedly or deliberately failed to comply with pertinent FDA regulations or repeatedly or deliberately submitted false information to FDA or the sponsor of the clinical trial in a required report.²³ Sub-investigators and study coordinators cannot be disqualified by FDA under current regulations. FDA initiates disqualification proceedings based on allegations of misconduct detected during an inspection of a clinical investigator.²⁴ Before issuing a NIDPOE letter, FDA staff evaluate information gathered during the inspection, obtain additional clarifying information as necessary (including, in some cases, information obtained from other inspections), determine whether their observations provide a foundation for initiation of a disqualification proceeding, and, if so, draft the NIDPOE letter with input from FDA's Office of the Chief Counsel. The misconduct alleged in the NIDPOE letter may have occurred years before the inspection.

²²As of June 18, 2009, FDA had not terminated debarment for any clinical investigators, sub-investigators, or study coordinators.

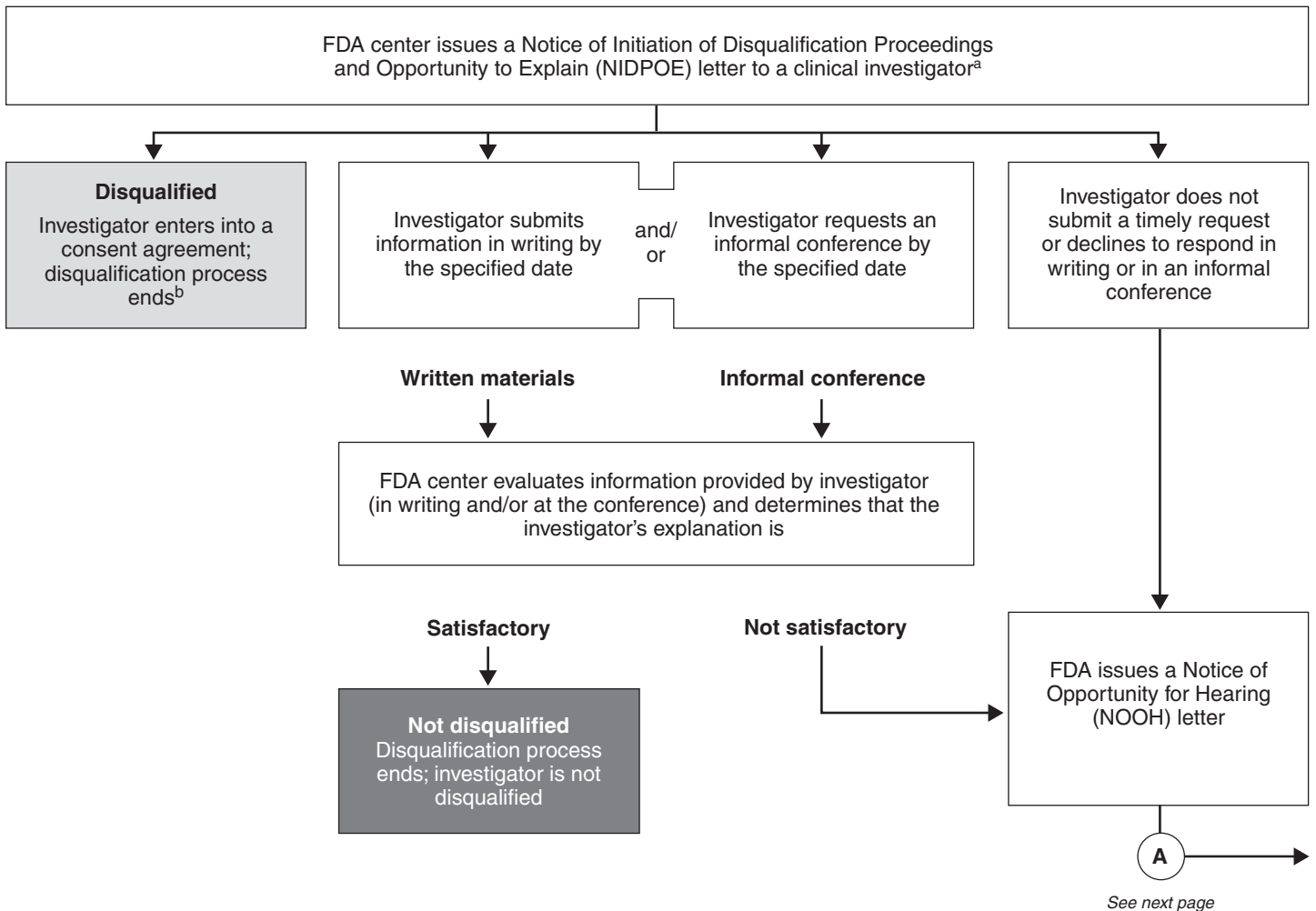
²³21 C.F.R. §§ 312.70, 812.119 (2008).

²⁴FDA conducts inspections of clinical investigators as part of its program to monitor the conduct of research involving investigational medical products.

As shown in figure 2, FDA's disqualification process involves multiple possible steps. FDA initiates a disqualification proceeding against a clinical investigator by providing the investigator with a NIDPOE letter.²⁵ The NIDPOE letter details FDA's allegations of misconduct and provides the investigator an opportunity to respond in writing or to meet informally with FDA officials to discuss the allegations. It also provides the investigator with the option of concluding the disqualification proceeding by entering into a consent agreement with FDA. The investigator and FDA may enter a consent agreement at any time before the Commissioner reaches a decision.

²⁵According to FDA officials, the agency typically initiated disqualification proceedings before 1998 without issuing a NIDPOE letter. If FDA determines that the investigator's misconduct could pose an ongoing risk to the safety and welfare of clinical trial participants, it can take steps to suspend or restrict the study, thereby limiting that investigator's research activities. FDA posts a list of investigators to whom it has issued a NIDPOE letter on its Web site, allowing sponsors and others to learn of the allegations of misconduct, and it notifies relevant sponsors and institutional review boards when a clinical investigator is disqualified. Other entities—such as sponsors of clinical trials or institutional review boards—may also take action to terminate a clinical trial or an investigator's participation in it after misconduct has been identified. See 21 C.F.R. §§ 56.113; 312.42(a), (b)(i); 312.56(b) (2008).

Figure 2: FDA's Disqualification Process for Clinical Investigators



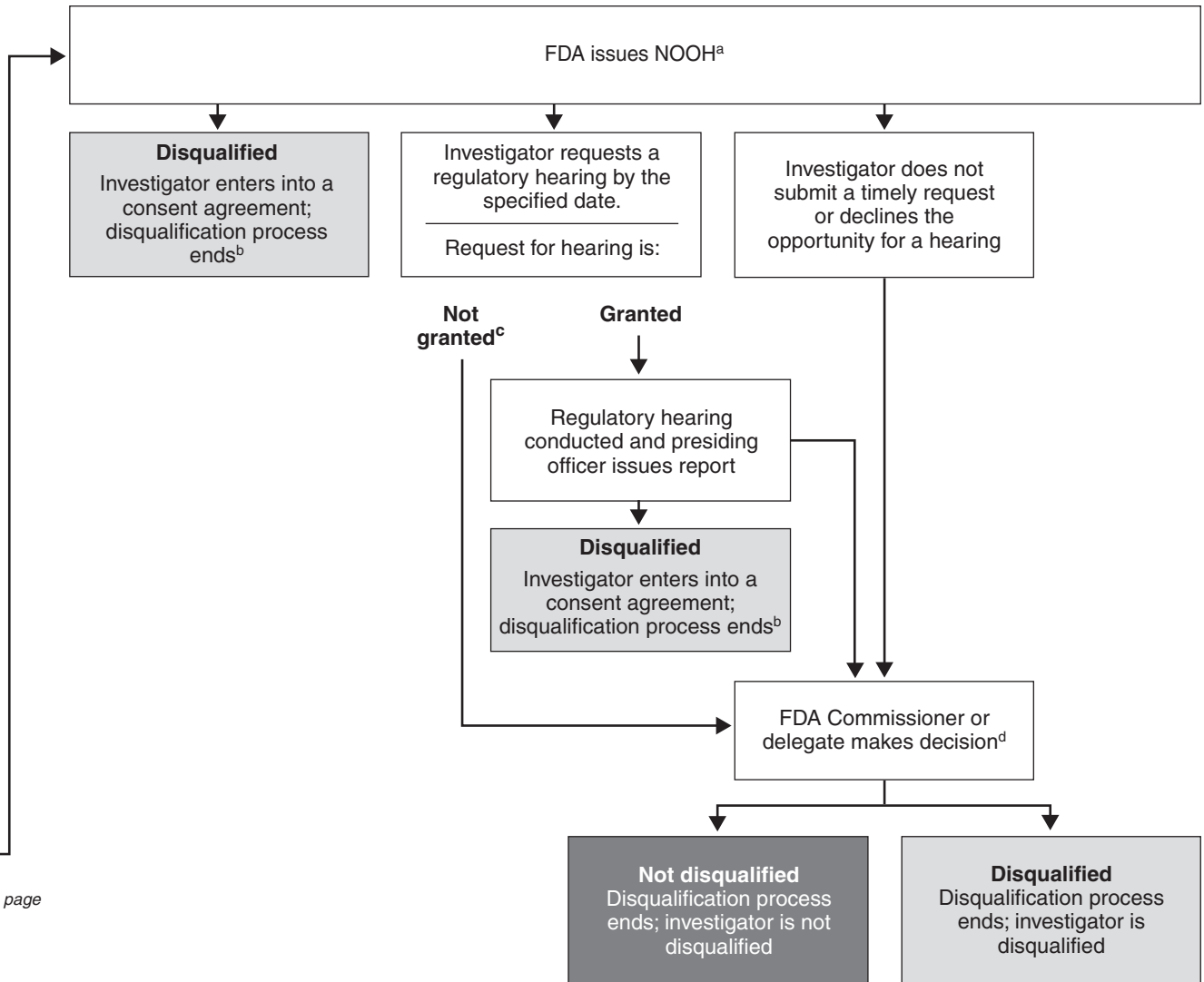
Source: GAO.

Notes: This figure presents the major steps that could be involved in disqualification proceedings we reviewed that were initiated by FDA using a NIDPOE letter from January 1, 1998, through September 9, 2008. The number of steps involved for a proceeding can vary depending, for example, on whether the individual chooses to contest the charges by requesting a hearing. For the purposes of this report, we treat consent agreements that restrict clinical investigators' activities as a form of disqualification.

^aNIDPOE letters specify that if the clinical investigator chooses to respond, he or she must request an informal conference or indicate an intention to submit a written reply within 15 days and provide the written reply within 30 days of receiving the letter.

^bThe clinical investigator and FDA may enter into a consent agreement, terminating the disqualification process, at any time before the Commissioner reaches a decision.

Figure 2 (cont.): FDA's Disqualification Process for Clinical Investigators



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See previous page

Source: GAO.

^aNotice of Opportunity for Hearing (NOOH) letters specify that if the clinical investigator chooses to request a regulatory hearing, he or she must do so within 10 business days of receiving the letter.

^bThe clinical investigator and FDA may enter into a consent agreement, terminating the disqualification process, at any time before the Commissioner reaches a decision.

^cWhen a request for a hearing is denied, the FDA Commissioner (or delegate) issues a decision that includes both a denial of the hearing and a notice of disqualification.

^dPrior to rendering a decision, the Commissioner (or the Commissioner's delegate) may, on his or her own initiative or at the request of the clinical investigator or center, review a decision by the presiding officer to deny a hearing, or to deny review of a particular issue during a hearing, because there is no genuine and substantial issue of fact to be resolved.

If the clinical investigator provides a timely explanation in response to a NIDPOE letter in a written response or in an informal conference, the investigator's explanation is evaluated by the FDA center (CDER for drugs, CBER for biologics, or CDRH for devices) that initiated the disqualification proceeding and the center's legal counsel. To evaluate the information presented by the investigator, FDA staff may collect additional information (which could include conducting an additional inspection). If the center finds the investigator's explanation for all of the allegations in the NIDPOE letter satisfactory, the disqualification proceeding is concluded and the investigator is not disqualified. Otherwise, FDA provides the investigator with an opportunity for a regulatory hearing to show why he or she should not be disqualified by issuing a Notice of Opportunity for Hearing (NOOH) letter, which details the allegations of misconduct that were included in the NIDPOE letter to which the investigator did not provide a satisfactory explanation.²⁶ If the investigator requests a hearing, he or she must submit evidence of a genuine and substantial issue of fact that would warrant a regulatory hearing. FDA evaluates this information and determines whether to grant a hearing or not. If the Commissioner determines that there is no genuine and substantial issue of fact, then he or she denies the request for a hearing and decides whether to disqualify the investigator. If a regulatory hearing is held, a presiding officer issues a report with a recommendation to the Commissioner, who makes the final decision about whether to disqualify the investigator. The presiding officer and Commissioner are assisted by FDA attorneys who are not associated with the center that initiated the disqualification proceeding.

Clinical investigators who are disqualified through a Commissioner's decision (without entering into a consent agreement) are disqualified from receiving either investigational drugs and biologics or investigational devices, depending on the type of product with which the misconduct was associated. For those investigators who are disqualified through a consent agreement, because the investigator may negotiate the terms of disqualification with FDA, the terms of such consent agreements vary and

²⁶Regulatory hearings conducted in the course of disqualification proceedings are conducted under part 16, Title 21, Code of Federal Regulations (2009).

may include restrictions on the investigator's research activities.²⁷ For example, the negotiated consent agreement might allow the individual to continue as a clinical investigator, but limit the number of clinical trials in which the investigator can participate at any one time. Disqualification does not preclude serving as a sub-investigator or study coordinator unless the terms of the consent agreement include such restrictions.

Clinical investigators who have been disqualified may apply to be reinstated as eligible to again receive investigational medical products. If disqualification was through a Commissioner's decision, disqualification is permanent unless the clinical investigator requests reinstatement, and the Commissioner determines that the investigator has presented adequate assurances that the investigator will use investigational medical products in compliance with pertinent FDA regulations.²⁸ If the investigator's disqualification was based on a consent agreement that restricted the investigator's activities for a specified period of time, reinstatement requires FDA's determination that the investigator met the terms of the consent agreement.

For additional information about debarment and disqualification, see appendix II.

²⁷For the purposes of this report, we consider agreements that restrict clinical investigators' activities as a form of disqualification and we treat attempts to negotiate the terms of a consent agreement as a form of contesting disqualification. In determining whether to agree to restrictions to a clinical investigator's activities, FDA officials told us that they consider what will best ensure the protection of clinical trial participants and the integrity of the resulting data.

²⁸21 C.F.R. §§ 312.70(f), 812.119(f) (2008).

**More than Half of
Debarment
Proceedings Took 4 or
More Years, and Type
of Debarment
Pursued, Internal
Control Weaknesses,
and Competing
Priorities Contributed
to Longer
Proceedings**

More than half of the debarment proceedings we reviewed took 4 or more years, and permissive proceedings generally took longer than mandatory proceedings. Factors such as internal control weaknesses and competing priorities were associated with longer proceedings. The agency has made or plans to make changes to its debarment policies and procedures that may improve the timeliness of debarment proceedings, but the effect of these changes remains to be seen.

**More than Half of
Debarment Proceedings
Took 4 or More Years**

The 18 debarment proceedings we reviewed took from just over 1 year to more than a decade, with more than half taking 4 or more years.²⁹ Of these 18 debarment proceedings—which were all of the proceedings FDA pursued or considered pursuing against clinical investigators, sub-investigators, and study coordinators since FDA obtained debarment authority in 1992—FDA completed 11 proceedings as of November 5, 2008. As shown in figure 3, the length of time to complete these 11 debarment proceedings—from an individual’s conviction through the publication of a debarment order in the *Federal Register*³⁰—ranged from just over 1 year to

²⁹See app. III for additional information about the debarment proceedings we reviewed and app. IV for information about the misconduct cited in proposal to debar letters.

³⁰For two proceedings in which the individual’s conviction occurred before FDA received debarment authority, we calculated the length of time from the date when FDA received debarment authority—May 13, 1992.

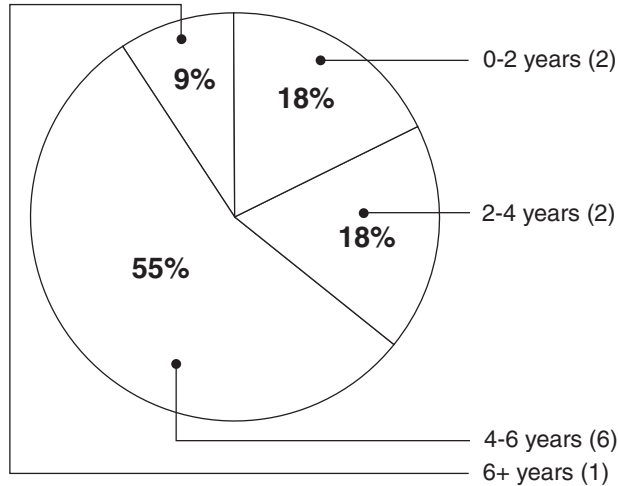
just over 6 years, with a median of 4.4 years.³¹ In addition to these 11 completed proceedings, FDA was pursuing or considering pursuing debarment for 7 clinical investigators and study coordinators. The length of time taken for these seven pending debarment proceedings—from an individual’s conviction through the last day of our file review—ranged from just over 1 year to nearly 11 years, with a median of 3.3 years.³²

³¹In one completed debarment proceeding that involved a study coordinator, FDA rescinded a debarment order after the agency learned that it had sent the proposal to debar letter to a different person with the same name as the study coordinator. By the time that FDA learned that the proposal to debar letter had been sent to the wrong person, the agency had already published a debarment order and just over 5 years had elapsed from the date of the study coordinator’s conviction. By law, FDA has 5 years from the date of an individual’s conviction to initiate a debarment action, and FDA initiates actions by notifying the individual of the proposed debarment. After considering the possibility of re-issuing a proposal to debar letter to the correct individual, FDA chose not to pursue debarment against the correct individual and rescinded the published debarment order. In our analysis, we treated this proceeding as completed and calculated that it took about 5 years from conviction to FDA’s publication of the debarment order.

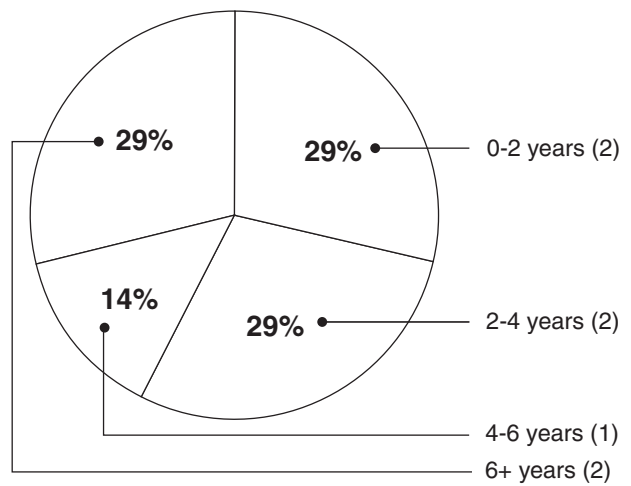
³²After we completed our review of FDA’s debarment files, FDA debarred the individuals involved in five of the seven pending debarment proceedings. As of September 1, 2009, two of the debarment proceedings in our review remained pending.

Figure 3: Time Taken for Completed and Pending Debarment Proceedings

Completed debarment proceedings (11 proceedings)



Pending debarment proceedings (7 proceedings)



Source: GAO analysis.

Notes: This figure presents, for clinical investigators, sub-investigators, and study coordinators, the length of time from conviction to completion for the 11 completed debarment proceedings and the length of time from conviction to November 5, 2008, for the 7 pending debarment proceedings. For two completed proceedings, the length of time was measured from the date when FDA received debarment authority (May 13, 1992) to completion because the clinical investigator was convicted before FDA received debarment authority. None of the debarment proceedings we reviewed took exactly 2 years or any exact multiple of 2 years to complete. Numbers of proceedings are shown in parentheses. Percentages for pending debarment proceedings do not add up to 100 percent due to rounding.

Debarment Proceedings Generally Took Longer If They Involved Permissive Debarment or If the Individual Contested Debarment

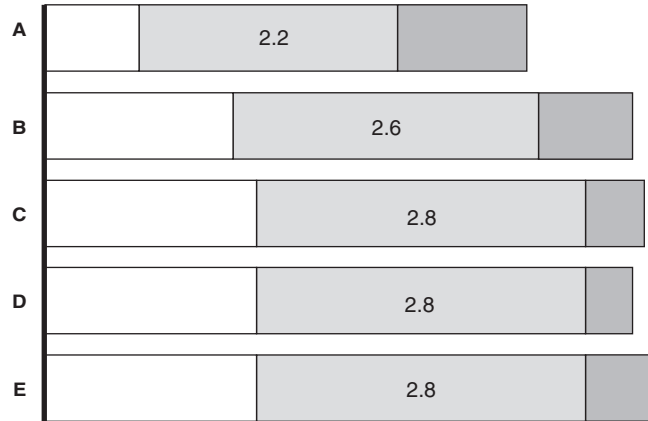
We found that permissive debarment proceedings generally took longer than mandatory proceedings. Of the 11 completed debarment proceedings, 5 were permissive debarment proceedings that took 4 or more years from conviction to debarment, with a median of 5.0 years. In contrast, six completed mandatory debarment proceedings took from just over 1 year to just over 6 years from conviction to debarment, with a median of 3.1 years. As shown in figure 4, the greatest difference between permissive and mandatory debarments was in the time it took to draft the proposal to

debar letter. For each permissive proceeding, FDA took more than 2 years from when the agency began drafting the proposal to debar letter to issuance of the proposal; for each of the five mandatory proceedings for which FDA recorded the date on which it began drafting the proposal to debar letter, this step took less than 9 months.³³

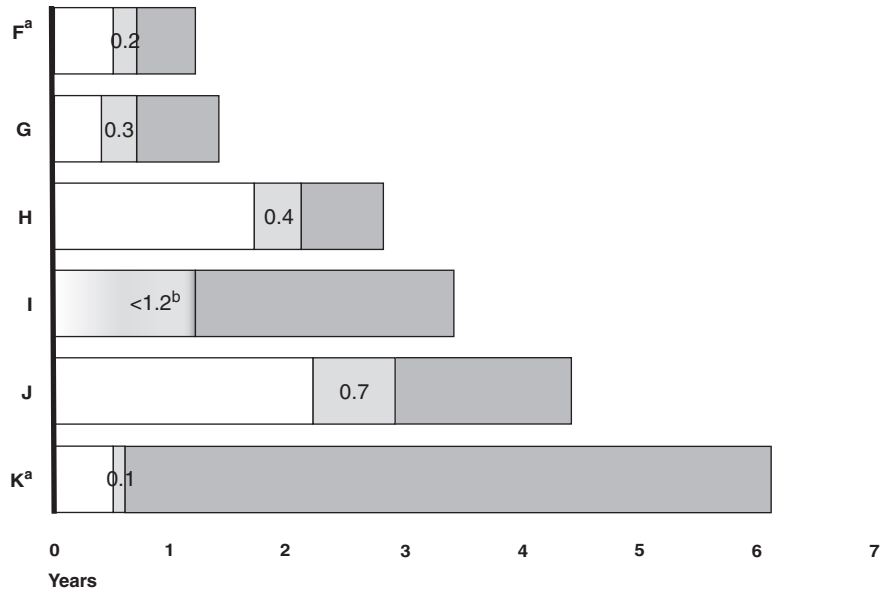
³³FDA's file for one proceeding involving mandatory debarment did not indicate when FDA began drafting the proposal to debar letter.

Figure 4: Lengths of Time for the 11 Completed Debarment Proceedings by Type of Debarment

Permissive proceedings



Mandatory proceedings



Conviction to initial draft of proposal to debar letter
 Initial draft of proposal to debar letter to issuance of proposal to debar letter
 Issuance of proposal to debar letter to debarment order

Source: GAO analysis.

Notes: Proceedings A through E represent five completed permissive debarment proceedings and proceedings F through K represent six completed mandatory debarment proceedings for clinical investigators, study coordinators, and a sub-investigator. For each proceeding, the amount of time taken (in years) from FDA's initial draft of the proposal to debar letter to issuance of the letter is presented.

^aThe date on which FDA received debarment authority, May 13, 1992, was used instead of the conviction date to calculate the length of time from conviction to the initial draft of the proposal to debar letter because the individual was convicted prior to May 13, 1992.

^bFDA's file for this proceeding did not indicate when FDA began drafting the proposal to debar letter. FDA took 1.2 years from conviction to FDA's issuance of the proposal to debar letter, so the time that elapsed from FDA's initial draft of the proposal to debar letter to issuance of the letter was less than 1.2 years.

According to FDA officials, the difference in the times taken between permissive and mandatory proceedings, including the difference in the times taken to draft proposal to debar letters, reflects the complexity of the statute and necessary analysis, including deciding the period of permissive debarment. FDA officials told us that the statutory standard for permissive debarment is more complex than the statutory standard for mandatory debarment, and that it may take more time to determine how a situation involving misconduct relates to the statutory standard for permissive debarment. They told us that the need to conduct an extensive analysis of a state felony conviction to determine which counts could provide a basis for permissive debarment was one factor that contributed to the time that elapsed between FDA's initial drafting of the proposal to debar letter and the date on which the letter was issued in two permissive debarment proceedings. In one of the proceedings, just over 2.5 years elapsed between the initial draft of the proposal to debar letter and the date on which it was issued, and in the other proceeding, which was still pending as of the last date of our file review, nearly 3 years elapsed.

We also found that debarment proceedings in which the individual contested debarment generally took longer to complete.³⁴ Five of the 18 proceedings we reviewed involved individuals who responded to FDA's proposal to debar letter by requesting a formal hearing to contest debarment. These proceedings took from 6 months to about 6 years, with a median of 2.2 years, from FDA's issuance of a proposal to debar letter to

³⁴Although 5 of the 18 proceedings we reviewed involved individuals who contested debarment by requesting a formal hearing, FDA officials informed us that the agency has never granted a formal hearing in a debarment proceeding because no one has provided evidence demonstrating that there were disputed issues of material fact.

debarment.³⁵ In contrast, there were nine debarment proceedings in which the individual received a proposal to debar letter, but did not contest debarment. These took from nearly 6 months to 1.5 years, with a median of 9.6 months—about one-third of the time taken for the proceedings in which the individual requested a hearing—from FDA’s issuance of a proposal to debar letter to debarment.³⁶ For example, in one proceeding that took just over 6 years from conviction to debarment, the clinical investigator contested debarment by submitting a hearing request in which the individual raised constitutional arguments about FDA’s proposal to debar. In that proceeding, it took more than 5 years and 4 months for FDA to complete the proceeding after the individual submitted the hearing request. According to FDA officials, the need to evaluate these legal arguments contributed to the delay.

Internal Control Weaknesses and Competing Priorities Contributed to Longer Debarment Proceedings

FDA identified several factors that contributed to the length of time taken to complete the debarment proceedings we reviewed. These factors included a lack of systematic procedures to help ensure timely communication of information relevant to debarment (such as conviction information) and a lack of policies and procedures that established time frames for debarment actions. These factors are related to weaknesses in FDA’s internal controls for debarment proceedings. In addition, for almost all of the proceedings, FDA cited limited resources due to competing priorities as a factor that contributed to the length of time taken to complete the proceedings.

FDA did not have systematic procedures for ensuring timely communication of relevant information about individuals who were convicted of crimes that could serve as the basis for debarment. Internal control standards specify that information should be communicated to those who need it in a form and within a time frame that enables them to carry out their operational responsibilities. FDA, however, did not have systematic procedures for ensuring timely communication of information

³⁵One of the five proceedings in which the individual received a proposal to debar letter and requested a hearing was pending as of the last date of our file review. For this pending proceeding, the time that elapsed was calculated from the date on which FDA issued the proposal to debar letter to the last date of our file review.

³⁶Two of the nine proceedings in which the individual received a proposal to debar letter and did not request a hearing were pending as of the last date of our file review. For these pending proceedings, the time that elapsed was calculated from the date on which FDA issued the proposal to debar letter to the last date of our file review.

that could be relevant to debarment and the informal procedures for communicating such information were not effective. FDA officials told us that communication between the center staff responsible for debarment and other FDA staff having information on convictions that might serve as a basis for debarment occurred on an informal basis (for example, by sending an e-mail a few times a year to other FDA staff) and that such communication may not have been sufficient for obtaining relevant information in a timely manner. For example, FDA officials told us that the CDER staff responsible for debarment did not learn of one clinical investigator's December 2003 conviction (through a plea agreement) for submitting a fraudulent medical license to a sponsor (that subsequently submitted it to FDA) until August 2007, about 3 years and 9 months after the conviction. Other FDA staff, however, were aware of the investigator's conviction in 2003. The Office of Criminal Investigations had been involved in the investigator's conviction. In addition, as a part of the plea agreement, CDER entered into a consent agreement in which the investigator agreed to be disqualified from receiving investigational drugs and biologics (and other products).³⁷ When asked to explain why the staff responsible for debarment learned of the conviction years after other FDA staff, FDA officials said that there may have been confusion about which CDER staff should obtain conviction information and that such confusion may have contributed to this delay. After we completed our file review, FDA issued a proposal to debar letter to the investigator on November 26, 2008, about 1 year and 3 months after CDER staff responsible for debarment learned of the conviction, and published a debarment order in the *Federal Register* on June 12, 2009. Although the investigator, who was not incarcerated, was disqualified from serving as a clinical investigator for drugs, biologics, devices, and other FDA-regulated products, the investigator was not prohibited by FDA from being involved in research in any other capacity (for example, as a sub-investigator or study coordinator) until the investigator was debarred in June 2009.

FDA officials involved with debarment told us that debarment proceedings were also delayed because FDA did not have established time frames for its completion of its actions in debarment proceedings. Implementation of appropriate policies and procedures to mitigate risks (such as the risk associated with failure to debar someone in a timely way) is one element of establishing appropriate internal controls. The only time frame related

³⁷The consent agreement was signed by the investigator in September 2003 and by a CDER official in May 2004.

to FDA's completion of any action involved in a debarment proceeding at the time of our file review was the statutory limit requiring that a debarment action be initiated within 5 years of a date of conviction.³⁸ As a result, FDA officials lacked common expectations about how long completion of specific actions should take, expectations that would establish a basis for them to elevate concerns if actions were not completed in a timely manner. For example, if center staff became concerned about the length of time the Office of the Chief Counsel was taking to review a draft proposal to debar letter, they had no written time frames against which to compare the time taken, and no clearly established basis for elevating their concern about the time taken to facilitate completion of that review.

In addition to factors related to internal control weaknesses, FDA officials told us that limited resources for debarment actions due to competing priorities contributed to the length of time taken for debarment proceedings. For 14 of the 18 proceedings we reviewed, FDA officials told us that the proceeding was delayed because of competing priorities. For example, they said that the officials responsible for drafting the proposal to debar letters had other responsibilities, including drafting regulations and responding to citizen petitions. They also said that the Office of the Chief Counsel's review of key documents, such as debarment orders, was delayed because of competing responsibilities, such as participating in litigation. FDA officials told us that competing priorities in CDER or the Office of the Chief Counsel likely contributed to several gaps of time with no recorded activity in its longest debarment proceeding involving a clinical investigator. The investigator was convicted of 53 counts of criminal offenses under state law in December 1997 for misconduct that included bribing an employee to conceal information about the attempted suicide of a clinical trial participant and prescribing a controlled substance without a license. This proceeding included a period of more than 4 years and 8 months in which our review of FDA's files revealed no documented activity. This proceeding was still pending in November 2008—nearly 11 years after the investigator was convicted and nearly 6 years after he was released from prison in 2003.³⁹ As a result, FDA had not debarred the investigator (which would have prohibited the investigator from

³⁸21 U.S.C. § 335a(1)(2).

³⁹We found that about 5 years elapsed between the individual's conviction and FDA's issuance of the proposal to debar letter and about 6 years had elapsed between FDA's issuance of the proposal to debar letter and the last day of our file review.

involvement with any entity that that has an approved or pending application for drugs or biologics) since his release from prison.⁴⁰

FDA Has Recently Made or Planned Changes to Its Debarment Policies and Procedures That Could Improve Timeliness

FDA has recently made changes to its debarment policies and procedures that could improve the timeliness of both permissive and mandatory debarment proceedings. In the spring of 2008, recognizing the need to improve FDA's debarment process, including the timeliness of debarment proceedings, FDA established the Debarment Working Group to examine its debarment procedures and identify ways to improve them. As a result of that effort, FDA took steps to strengthen its internal controls by issuing a new staff manual guide in March 2009 and new standard operating procedures in April 2009.⁴¹ The staff manual guide establishes systematic procedures for timely communication of relevant information and time frames for completion of its actions in debarment proceedings. The changes in FDA's debarment policies and procedures include the following:

- FDA established systematic procedures to facilitate timely communication of information about potentially relevant convictions. Under the new staff manual guide, the Office of Enforcement is responsible for establishing procedures in cooperation with other relevant FDA components, including

⁴⁰FDA disqualified this clinical investigator through a consent agreement as required by the investigator's plea agreement. Although the individual was disqualified in February 1999 from receiving investigational drugs and biologics as a clinical investigator and from serving as a sub-investigator or an assistant in the clinical segment of a clinical study involving investigational drugs or biologics, this disqualification does not prevent him from participating in clinical research in some other capacity.

⁴¹FDA has also taken other actions to improve its procedures related to debarment proceedings. After we found that FDA's public debarment list—the list available on FDA's Web site that is used by individuals or corporations that have an approved or pending drug application and others to identify individuals who have been debarred by FDA—contained a misspelling of the name of an individual who was debarred on July 26, 1993, the Office of Enforcement established new procedures to improve its process for approving and publishing debarment information on FDA's Web site in October 2008. During the time that the debarred individual's name was misspelled on the Web site, if an individual or corporation that had an approved or pending drug application searched the list for the debarred individual's name, they would not have found a match and would not have learned of his debarment. After we notified FDA officials of the misspelling, FDA officials said that FDA corrected the spelling on the Web site on September 22, 2008. In January 2009, FDA officials informed us that they had no indication that this debarred individual has worked in a position that would violate the terms of debarment and they had no plans to investigate his employment. FDA's new procedures for approving and publishing FDA's public debarment list on FDA's Web site include procedures for periodically assessing the accuracy of published information.

the Office of Criminal Investigations, and with the Department of Justice to facilitate the communication of information about convictions and misconduct relevant to debarment more systematically. The official in the Office of Enforcement who will oversee implementation of the new staff manual guide policies and procedures told us in April 2009 that the Office of Enforcement had put in place procedures to obtain conviction information from the Office of Criminal Investigations and the Department of Justice. Furthermore, according to the staff manual guide, the Office of Criminal Investigations is to provide quarterly reports to the Office of Enforcement that include all convictions occurring within the preceding 3 months that may serve as a basis for debarment. The Office of Enforcement official told us that the quarterly reports from the Office of Criminal Investigations are to cover those convictions in which the Office of Criminal Investigations was involved and sentencing has occurred. In addition, the staff manual guide states that all FDA employees are responsible for informing the Office of Enforcement as soon as possible when they become aware of any individuals who may be subject to debarment. FDA officials said that after the staff manual guide was finalized and published, the Office of Enforcement announced this requirement to FDA employees. They also said that the Office of Enforcement may further formalize this requirement in FDA's regulatory procedures manual.

- FDA established time frames for completing debarment actions. The new staff manual guide for debarment establishes new policies and procedures that include time frames to help ensure faster completion of debarment proceedings.⁴² For example, the staff manual guide states that FDA is to complete a debarment proceeding in which an individual fails to respond to a proposal to debar letter within 350 calendar days of the individual's

⁴²The staff manual guide specifies that the time frames will not become effective until FDA clears an initial backlog of potential debarment proceedings. FDA officials, including the official in the Office of Enforcement responsible for leading that office's efforts to identify relevant convictions and initiate debarment proceedings, told us that as of June 2009 they had received information from the Office of Criminal Investigations and had identified more than 1,600 individuals with potentially relevant convictions. FDA officials said, however, that they had not yet identified the roles of the individuals or determined whether their convictions provide a basis for debarment. They said that pursuing debarment for individuals with convictions involving misconduct with a clear impact on the drug or biologic approval process or who are working for a company that has submitted a drug or biologic application to FDA will be the Office of Enforcement's highest priority and that they estimate clearing the backlog of such individuals within 6 months using the time frames set forth in the staff manual guide. FDA officials said that the estimate is based on a number of factors, including the availability of a staff member to work exclusively on debarment proceedings.

conviction. Although there are no consequences specified in the staff manual guide for failing to meet the new time frames, FDA officials said that they believe that drawing attention to time frames will help ensure more timely debarment proceedings and provide a basis for action to expedite them. In addition, the staff manual guide reassigns responsibilities for debarment proceedings that had belonged to CBER and CDER to the Office of Enforcement. Since March 2009, the Office of Enforcement's responsibilities include (among other things) determining whether to initiate debarment actions, preparing and issuing proposal to debar letters, consulting with CDER and CBER to determine whether to pursue permissive debarment, working with officials from the Office of the Chief Counsel on legal matters, and preparing and issuing debarment orders (when a hearing request is not involved). The official in the Office of Enforcement who will oversee implementation of the new staff manual guide policies and procedures said that the establishment of time frames for debarment actions provides a basis for the Office of Enforcement to elevate any concerns that arise about the times taken and facilitate completion of those actions. This official said that this office will, for example, monitor the amount of time being taken by the Office of the Chief Counsel to review a draft proposal to debar letter to help ensure that the Office of the Chief Counsel is meeting the time frame (30 days) specified in the new staff manual guide for reviewing such documents. If the time frame is not met, the Office of Enforcement official plans to use the staff manual guide as a basis for raising the issue to other appropriate officials.

FDA officials said that they are planning other changes to FDA's debarment policies and procedures. They said that the Office of Enforcement is considering additional changes in standard operating procedures. In addition, to help implement the new policies and procedures, the official in the Office of Enforcement who will oversee their implementation said that the office plans to employ a full-time staff member whose primary responsibility will be to work on debarment proceedings. According to the new standard operating procedures, the staff member's responsibilities will include obtaining conviction information, gathering information to help determine whether to pursue debarment, and coordinating the issuance of proposal to debar letters.

FDA's changes or planned changes in its debarment policies and procedures—including the steps taken to strengthen internal controls—could reduce the length of time taken to complete debarment proceedings, but the effects of these changes remain to be seen. Meeting the time frames will require FDA to complete the debarment process in a

significantly shorter length of time than it took to complete the process in the debarment proceedings we reviewed. For example, the new time frame to complete a debarment proceeding in which an individual fails to respond to a proposal to debar letter is 350 calendar days from an individual's conviction. However, FDA took longer than 350 calendar days from conviction to debarment in all 7 completed proceedings in our review that did not include a hearing request, with 5 of the proceedings taking more than 4 years. In addition, it remains to be seen whether FDA will be able to focus or add to its limited resources on debarment proceedings. For example, although the official in the Office of Enforcement who will oversee implementation of the new staff manual guide policies and procedures told us that they plan to employ a full-time staff member whose primary responsibility will be to work on debarment proceedings, as of June 2009 the permanent position had not yet been filled.⁴³ Finally, it is not yet clear whether the Office of the Chief Counsel will have sufficient resources available for assisting with debarment proceedings in a timely manner. An official in the Office of the Chief Counsel said that they did not expect any changes to the Office of the Chief Counsel's resources, unless the number of debarment proceedings increases substantially. According to FDA, the Office of the Chief Counsel regularly evaluates its resource needs and any significant increases in the number of debarments will be factored into those evaluations.

⁴³ According to the official in the Office of Enforcement who will oversee implementation of the new staff manual guide policies and procedures, the Office of Enforcement received clearance to fill this position in August 2009, but FDA had not filled the position as of September 1, 2009. While waiting for clearance of that announcement, FDA announced a temporary opening for an FDA employee to assume debarment-related responsibilities. This official told us that an FDA employee began acting in this temporary position in June 2009.

Times Taken for Disqualification Proceedings Varied and Factors Such as Clinical Investigators' Contesting Disqualification and Internal Control Weaknesses May Have Contributed to Longer Proceedings

The times taken for the disqualification proceedings we reviewed varied widely and were longer when the clinical investigator contested disqualification. Factors such as a lack of established time frames (an internal control weakness) and competing priorities may have contributed to the length of time taken to complete disqualification proceedings. The agency has made changes to its disqualification procedures that may improve the timeliness of disqualification proceedings, but the full effect of these changes remains to be seen.

About One-Third of Disqualification Proceedings Took 2 or More Years and Proceedings Were Completed More Quickly Over Time

The disqualification proceedings we reviewed varied widely in the time taken, with about one-third of the proceedings taking 2 or more years (see fig. 5).⁴⁴ Of the 52 proceedings we reviewed—which included all of the disqualification proceedings FDA initiated with a NIDPOE letter from January 1, 1998, through September 9, 2008—FDA completed 47 disqualification proceedings as of November 5, 2008. The length of time to complete these 47 disqualification proceedings—from issuance of a NIDPOE letter through disqualification or an FDA decision to terminate the proceeding—ranged from 26 days to more than 10 years, with a median of 1.1 years. In addition to these 47 completed proceedings, FDA initiated, but had not completed, 5 disqualification proceedings. The time taken for these 5 pending proceedings—from issuance of a NIDPOE letter through the last date of our file review—ranged from 70 days to more than 7 years and 4 months, with a median of 2.5 years.⁴⁵

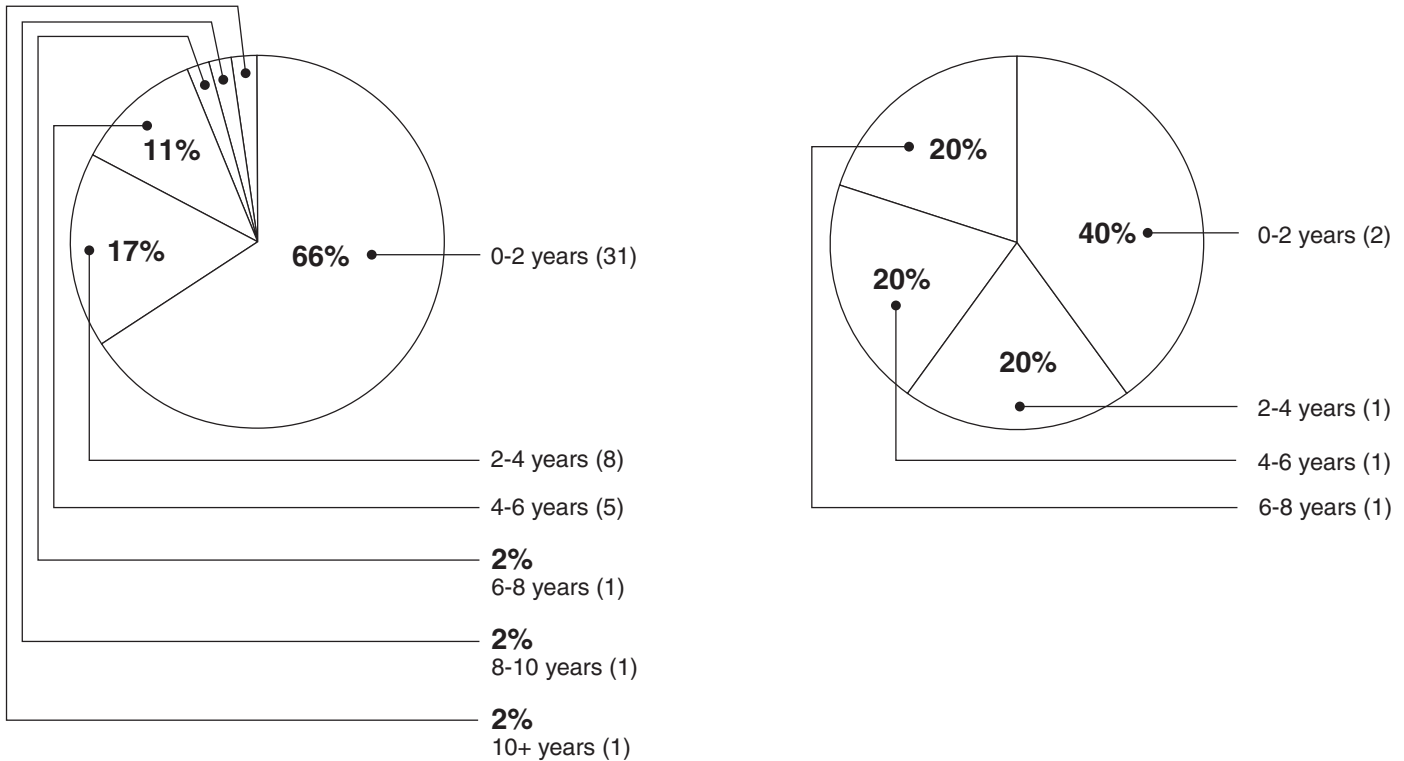
⁴⁴See app. V for additional information about the disqualification proceedings we reviewed and app. VI for information about the allegations of misconduct included in the NIDPOE letters used to initiate these disqualification proceedings.

⁴⁵We defined a disqualification proceeding as pending if, as of the last date of our file review (Nov. 5, 2008), FDA had issued a NIDPOE letter, but had not concluded the disqualification proceeding. After we completed our review of FDA's disqualification files, FDA disqualified the clinical investigators involved in three of the five pending disqualification proceedings. As of September 1, 2009, two of the disqualification proceedings in our review remained pending.

Figure 5: Time Taken for Completed and Pending Disqualification Proceedings

Completed disqualification proceedings (47 proceedings)

Pending disqualification proceedings (5 proceedings)

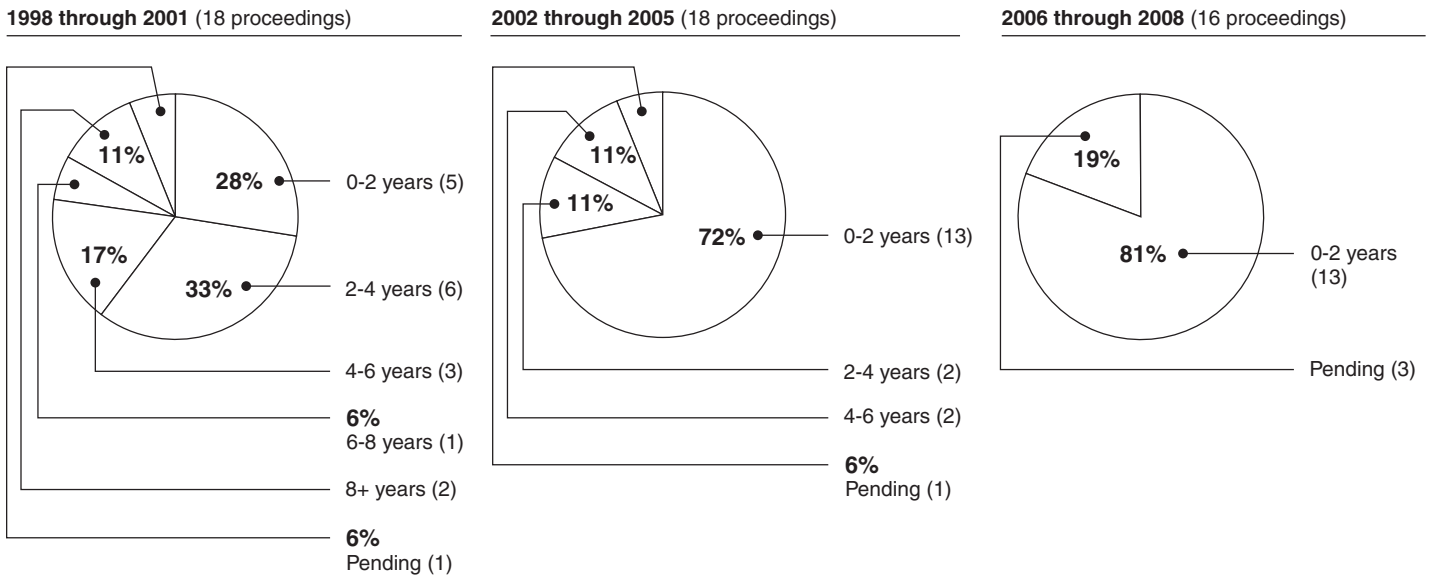


Source: GAO analysis.

Notes: This figure presents the length of time from issuance of the NIDPOE letter to completion for 47 completed disqualification proceedings (45 that ended in disqualification and 2 that did not) and the length of time from issuance of the NIDPOE letter to November 5, 2008, for 5 pending disqualification proceedings. All of these proceedings were initiated by a NIDPOE letter between January 1, 1998, and September 9, 2008. Numbers of proceedings are shown in parentheses. None of the disqualification proceedings we reviewed took exactly 2 years or any exact multiple of 2 years to complete.

We also found that FDA’s disqualification proceedings initiated by a NIDPOE letter in 1998 through 2001 generally took longer to complete than proceedings that were initiated more recently (see fig. 6, which also shows pending proceedings). Completed proceedings initiated in 1998 through 2001 took from just over 3 months to more than 10 years, with a median of 2.8 years. Completed proceedings initiated in 2002 through 2005 took from just over 1 month to more than 4 years and 8 months, with a median of 0.9 years. Completed proceedings initiated in 2006 through 2008 took from nearly 1 month to about 2 years, with a median of 0.5 years.

Figure 6: Time Taken for Disqualification Proceedings Initiated in 1998 through 2001, 2002 through 2005, and 2006 through 2008



Source: GAO analysis.

Notes: This figure presents the length of time from issuance of the NIDPOE letter to completion of the proceeding (if completed as of Nov. 5, 2008) or pending status (if pending as of Nov. 5, 2008) for 18 disqualification proceedings initiated by a NIDPOE letter in 1998 through 2001, 18 disqualification proceedings initiated by a NIDPOE letter in 2002 through 2005, and 16 disqualification proceedings initiated by a NIDPOE letter from January 1, 2006, through September 9, 2008. None of the disqualification proceedings we reviewed took exactly 2 years or any exact multiple of 2 years to complete. Numbers of proceedings are shown in parentheses. Percentages do not always add up to 100 due to rounding.

Factors Associated with Longer Disqualification Proceedings Included Whether the Clinical Investigator Contested Disqualification and Ongoing Criminal Cases

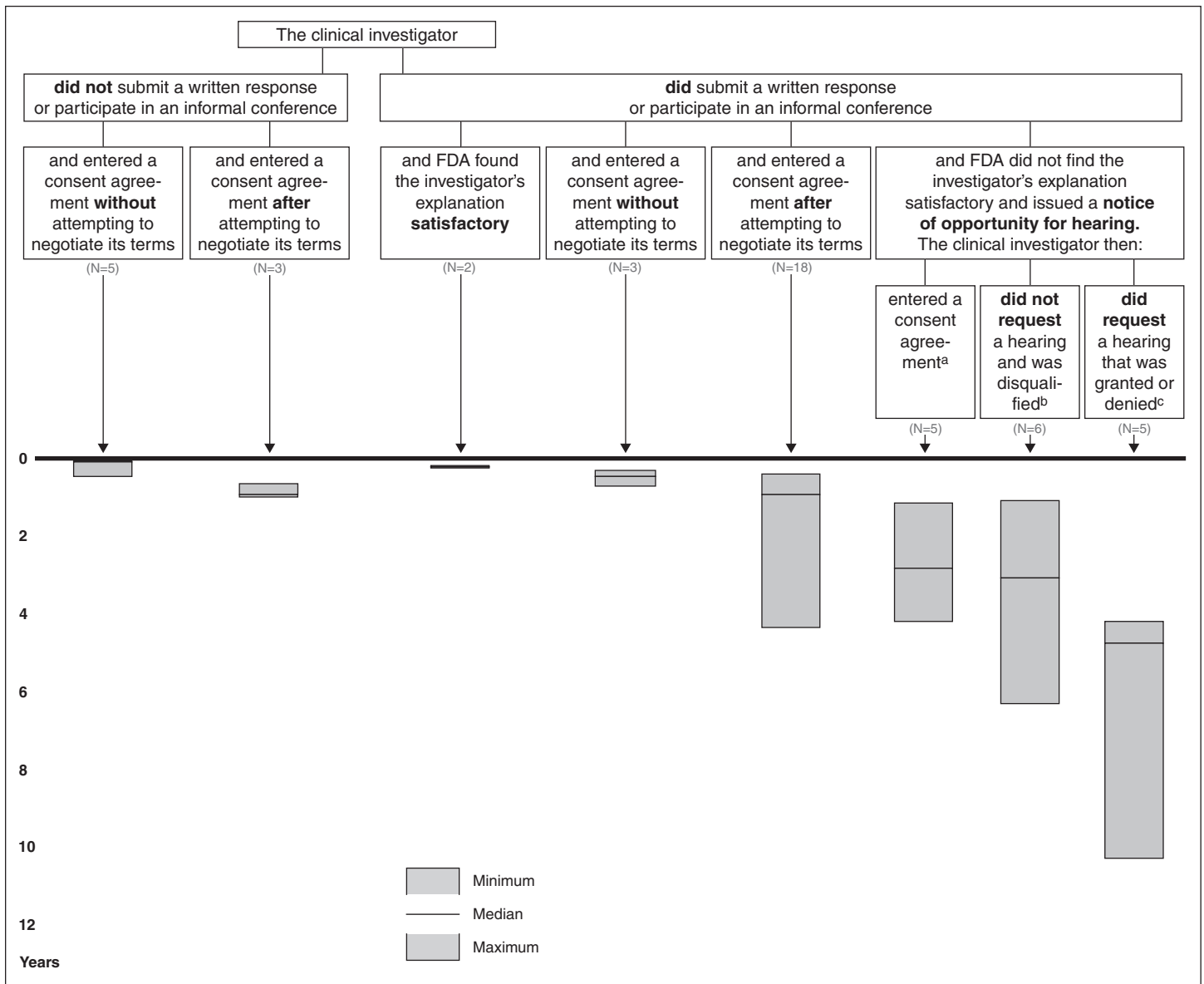
Factors associated with longer disqualification proceedings included whether the clinical investigator contested disqualification and ongoing criminal cases.

The more steps taken by the clinical investigator to contest disqualification, the longer it generally took to complete the proceeding (see fig. 7). As examples, disqualification proceedings generally took longer if the investigator contested disqualification by responding to the NIDPOE letter in a written response or informal conference, contested the terms of disqualification by attempting to negotiate the terms of a consent

agreement, or contested disqualification by requesting a hearing.⁴⁶ The two disqualification proceedings in our review in which FDA found the investigator's explanation satisfactory and did not disqualify the individual were concluded relatively quickly.

⁴⁶In one proceeding for which the clinical investigator requested a hearing, the investigator was prohibited from receiving investigational drugs, biologics, devices, and other FDA-regulated products as part of a plea agreement in a criminal proceeding. This investigator entered the plea agreement after an FDA hearing had begun and FDA continued the disqualification proceeding. FDA officials told us that they concluded that the terms of the plea agreement would not be enforceable after about 3 years. The presiding officer recommended disqualification, and the investigator requested a Commissioner's review. Just over 5 years after the investigator requested a Commissioner's review—9.5 years after issuance of the NIDPOE letter—FDA completed this disqualification proceeding with a Commissioner's decision to disqualify the investigator. We calculated the length of time this disqualification proceeding took from issuance of the NIDPOE letter to the date of the Commissioner's disqualification decision.

Figure 7: Time Taken to Complete Disqualification Proceedings



Source: GAO.

Notes: Data are for 47 disqualification proceedings initiated by a NIDPOE letter between January 1, 1998, and September 9, 2008, and completed as of November 5, 2008. There was one disqualification proceeding in which FDA issued a Notice of Opportunity for Hearing to a clinical investigator who had not presented information in writing or participated in an informal conference; this proceeding is included among the five proceedings in which a hearing was requested and either granted or denied.

^aThese five proceedings involved two investigators who entered into a consent agreement with FDA without requesting a hearing and three investigators who entered into a consent agreement after requesting a hearing but before FDA either denied or granted the request for a hearing.

^bThese six proceedings involved investigators who did not request a hearing and were disqualified by a Commissioner's decision.

^cThese five proceedings included one investigator whose request for a hearing was denied and who was disqualified by a Commissioner's decision. Also included are four investigators whose requests for a hearing were granted. After one investigator's hearing request was granted, the investigator agreed to restrictions on his research activities as part of a settlement agreement negotiated with the Department of Justice on behalf of FDA and other components of the Department of Health and Human Services. Another investigator entered into a consent agreement with FDA after the hearing was completed, but before the Commissioner reached a decision. The other two investigators whose requests for a hearing were granted were disqualified by a Commissioner's decision after completion of the hearing; these two cases took 9.5 and 10.2 years, respectively.

Another factor that contributed to longer proceedings was the suspension of disqualification actions during criminal cases related to the misconduct of the clinical investigators. For example, two of the five disqualification proceedings that were pending when we completed our file review were delayed for more than 2 years due to ongoing criminal cases. According to FDA officials, disqualification proceedings may be suspended during ongoing criminal cases for several reasons. Documents needed to support the disqualification proceedings (such as the medical records of clinical trial participants or forms prepared to document the conduct of the clinical trial) may be unavailable to FDA because they are in the custody of the United States Attorney as a result of the criminal investigation. In addition, FDA may be involved in negotiations to include, as part of a plea agreement, a consent agreement that would disqualify the investigator, and the disqualification proceeding may be delayed while conducting these negotiations. FDA may also agree to requests made by the clinical investigator or his or her legal counsel for additional time to respond to the disqualification proceeding so that he or she can focus on the criminal investigation.

Internal Control Weaknesses and Competing Priorities May Have Contributed to Longer Disqualification Proceedings

FDA officials told us that several factors contributed or may have contributed to the length of time taken to complete the disqualification proceedings that we reviewed. These factors included internal control weaknesses—specifically, a lack of appropriate policies and procedures to help ensure timely completion of disqualification actions by establishing time frames. In addition, FDA cited limited resources due to competing priorities and changes in personnel as factors associated with longer disqualification proceedings.

FDA told us that a lack of time frames for FDA's completion of disqualification proceedings might have contributed to longer proceedings. As with debarment proceedings, FDA officials lacked common expectations about how long completion of specific actions should take that would establish a basis for them to elevate concerns if actions were not completed in a timely manner. For example, if center staff became concerned about the length of time the Office of the Chief Counsel was taking to review a draft NOOH letter, they had no written time frames against which to compare the time taken and no clearly established basis for elevating their concern about the time taken to facilitate completion of that review.

In addition to an internal control weakness, FDA told us that limited resources in the Office of the Chief Counsel for disqualification actions due to competing priorities contributed to the length of time taken to complete some disqualification proceedings. For example, FDA told us that limited resources and competing priorities contributed to delays in one disqualification proceeding, including a delay of about 3 years and 9 months during which the clinical investigator's request for a review of the presiding officer's report was pending in FDA's Offices of the Chief Counsel and Commissioner. FDA also told us that limited resources and competing demands contributed to a delay of about 1 year and 4 months in one proceeding in which the terms of a consent agreement were being negotiated and a delay of just over a year in another proceeding in which a presiding officer was reviewing arguments for and against holding a regulatory hearing.

Changes in personnel also contributed to the length of time taken to complete certain disqualification proceedings. For example, in two proceedings we reviewed, regulatory hearings began with presiding officers who did not complete the hearings. As a result, new presiding officers had to be appointed and become familiar with the arguments of the cases, resulting in longer proceedings. In addition, FDA officials said that changes in center personnel, and the associated need to train new staff, contributed to some of the delays in completing disqualification proceedings that were initiated in the late 1990s and early 2000s.

FDA Has Made Changes to Its Disqualification Policies and Procedures That Could Improve Timeliness

FDA has taken steps to enhance the timeliness of disqualification proceedings by establishing new policies and procedures that include time frames for its completion of disqualification actions. Until June 2008, FDA did not have time frames for its completion of any of its disqualification actions. Recognizing the need to improve the timeliness of its disqualification proceedings, FDA issued a new staff manual guide in June 2008 that established time frames for disqualification actions that follow the issuance of a NOOH letter. In January 2009, FDA revised its regulatory procedures manual, establishing time frames for disqualification actions through and including issuance of a NOOH letter. Although no consequences are specified for failing to meet the new time frames, FDA officials said that they believe that drawing attention to time frames will help them ensure more timely disqualification proceedings and provide a basis for action to expedite them. In addition, FDA recently reassigned responsibility for monitoring the progress of all disqualification proceedings in which a NOOH letter has been issued to the Good Clinical Practice Program. The Good Clinical Practice Program began taking responsibility for these proceedings in spring of 2008, and hired a staff member to help oversee and monitor the disqualification process in June 2008.⁴⁷ Centers retain responsibility for initiating disqualification proceedings, evaluating responses from the clinical investigator, and determining whether to recommend issuance of a NOOH letter. The Good Clinical Practice Program is responsible for tracking the progress of all disqualification proceedings from issuance of the NIDPOE letter through completion and has created a database to do so. FDA officials told us that they believe that assigning monitoring responsibilities to the Good Clinical Practice Program should help ensure more timely completion of all disqualification proceedings. They told us that the establishment of time frames for disqualification actions provides a basis for elevating any concerns that arise about the time taken for actions and to facilitate completion of those actions.

FDA also told us that changes were made in recent years to provide additional resources for disqualification proceedings and that these changes have improved or will improve the timeliness of proceedings. For

⁴⁷Responsibility for disqualification proceedings that involved hearings had been assigned to the Office of Health Affairs until 1999 and to the Office of the Ombudsman from 1999 until responsibility was re-assigned to the Good Clinical Practice Program starting in spring of 2008. FDA officials told us that they re-assigned these responsibilities to the Good Clinical Practice Program because of that office's broader role within the agency as the focal point for issues arising in human research trials regulated by FDA.

example, the agency told us that CDER has improved the timeliness of the center's actions in disqualification proceedings because, since May 2006, additional CDER staff have been available to focus on initiating proceedings. In addition, the agency told us that over the past several years, the Office of the Chief Counsel increased its resources for drug matters, which resulted in an increase of resources for disqualification. According to FDA, the increase has enabled the office to handle more disqualification proceedings initiated by the centers and to handle more expeditiously the drafting and review of Commissioner's decisions.

FDA's changes in its policies and procedures for disqualification—including the steps taken to strengthen internal controls—could reduce the length of time taken to complete disqualification proceedings, but the full effect of these changes remain to be seen. Meeting the time frames would require FDA to complete some disqualification actions in a significantly shorter length of time than it took to complete these actions in some of the proceedings we reviewed. For example, the January 2009 regulatory procedures manual specifies that a NOOH letter should be issued within 11 working days of the time the center forwards a recommendation to issue it, and we found that at least 13 of the 17 proceedings we reviewed in which a NOOH letter was issued did not meet this time frame; instead, this step took more than 2 months in at least 5 proceedings. The June 2008 staff manual guide specifies that a presiding officer should issue a report within 90 days of a regulatory hearing. None of the three proceedings with presiding officer reports that we reviewed were issued within 90 days. They were issued after about 14.5 months, 23 months, and 42 months, respectively.⁴⁸ In addition, the January 2009 revisions to the regulatory procedures manual specify that a NIDPOE letter should be issued within about 9 and a half months of the inspection

⁴⁸These three presiding officer's reports were issued before FDA issued the staff manual guide specifying the 90-day time frame for issuance of presiding officer's reports.

that revealed misconduct, and about two-thirds of the 52 proceedings we reviewed did not meet this time frame.⁴⁹

FDA's Debarment Authority Does Not Fully Extend to Involvement with Devices and Regulations Allow Disqualified Clinical Investigators to Conduct Trials for Other Investigational Medical Products

FDA's oversight of clinical investigators, sub-investigators, and study coordinators is limited by two aspects of its statutory debarment authority and because FDA's regulations do not extend a clinical investigator's disqualification for investigational drugs and biologics to investigational devices and vice versa.

FDA's Debarment Authority May Not Permit FDA to Address Misconduct Related to Medical Devices

FDA's debarment authority may not permit FDA to address misconduct in two significant ways. First, although an individual may have been debarred from involvement with drugs and biologics, a debarred individual is not necessarily precluded from involvement with FDA-regulated products other than drugs and biologics, such as medical devices. For example, in one completed debarment proceeding that we reviewed, a study coordinator who was involved in drug research was debarred as a result of being convicted of a federal felony. This study coordinator admitted destroying X-ray film reports and falsifying electrocardiogram results. Despite debarment, this individual could still provide services for an entity

⁴⁹For the disqualification proceedings we reviewed, the length of time from the last day of the inspection to issuance of the NIDPOE letter ranged from 23 days to more than 4 years, with a median of just over 1 year. In response to recommendations by the Department of Health and Human Services's Office of Inspector General and to help improve the efficiency and consistency of its initiation of disqualification proceedings, FDA issued new guidance in December 2008 that clarifies the circumstances under which disqualification should be considered and specifies procedures for communication between the staff who conduct inspections and the staff who are responsible for initiating disqualification proceedings.

that markets or intends to market FDA-regulated products other than drugs or biologics, including medical devices.

Second, an individual may be debarred from involvement with drugs and biologics, but not from involvement with medical devices, regardless of the kind of misconduct in which the individual engaged. While the statute expressly authorizes FDA to debar an individual from involvement with drugs and biologics, there is no comparable authority with regard to an individual involved with medical devices. For example, one investigator who falsely advertised an unapproved investigational laser device for treating eye disorders as an FDA-approved device, and who falsified information in the medical records of patients treated with the device cannot be debarred by FDA from working in the medical device industry.⁵⁰ A CDRH official told us that he would like FDA to have the authority to debar individuals like this investigator. When asked whether the agency had pursued obtaining this authority, the agency responded that the Office of the Chief Counsel was not aware of any efforts to expand FDA's debarment authority, but did not provide a reason for not requesting this authority.

FDA's Regulations Allow Disqualified Clinical Investigators to Conduct Trials for Other Medical Products

FDA's disqualification regulations are included in two separate sets of regulations—one for drugs and biologics and another for devices—and both sets of regulations limit the types of products to which disqualification applies.⁵¹ As a result, FDA's oversight of clinical investigators is limited. Under federal regulations, an investigator who is disqualified by a Commissioner's decision for misconduct related to drugs or biologics is still able to serve as an investigator for devices, and an investigator who is disqualified by a Commissioner's decision for misconduct related to devices is still able to serve as an investigator for drugs and biologics. Moreover, an investigator who is disqualified by a Commissioner's decision for misconduct related to drugs, biologics, or devices is still able to serve as an investigator for other FDA-regulated investigational products, such as animal drugs and food additives. Of the nine completed proceedings we reviewed that resulted in disqualification by a Commissioner's decision (instead of a consent agreement), eight

⁵⁰FDA disqualified this individual from receiving investigational devices as a clinical investigator and imposed a civil money penalty on the individual and his company of \$1.1 million. This individual continued to function as a sponsor of an FDA-regulated device.

⁵¹21 C.F.R. §§ 312.70 (drugs and biologics), 812.119 (devices) (2008).

investigators were disqualified from receiving investigational drugs and biologics, but not devices, and one investigator was disqualified from receiving investigational devices, but not drugs or biologics. For example, one disqualified investigator (who, among other things, falsely reported that investigational vaccines had been administered to infants when they had not and failed to report that some clinical trial participants had been hospitalized) is prohibited from being an investigator for drugs or biologics, but is not disqualified from receiving medical devices or other FDA-regulated investigational products, and so can serve as an investigator for research on these products should this individual choose to do so.⁵²

Compared to disqualifications that resulted from a Commissioner's decision, FDA has more latitude in determining the consequences of disqualification when it results from a consent agreement between FDA and the investigator. Of the 35 completed proceedings we reviewed that resulted in disqualification through consent agreements,⁵³

- Fifteen consent agreements contained more extensive restrictions by disqualifying the investigator from receiving any FDA-regulated investigational products (including drugs, biologics, devices, animal drugs, and food additives). For example, FDA concluded that one investigator failed to obtain required informed consent, failed to document that women were not pregnant before being given an investigational drug, and submitted false information. This investigator entered into a consent agreement with FDA that disqualified him from receiving any FDA-regulated investigational products, including drugs and biologics, as well as medical devices. If the investigator had been disqualified by a Commissioner's decision, he could not have been disqualified from receiving medical devices or FDA-regulated investigational products other than drugs and biologics.
- Nineteen consent agreements contained terms that restricted the investigator's research activities in ways that differed from what would have resulted from a Commissioner's decision. These consent agreements

⁵²See app. V for more information about the products that clinical investigators were disqualified from receiving.

⁵³In addition to disqualifications based on decisions by the Commissioner or consent agreements, one clinical investigator agreed to restrictions on his research activities as part of a settlement agreement negotiated with the Department of Justice on behalf of the FDA and other components of the Department of Health and Human Services. Also, FDA found the explanations offered by two clinical investigators satisfactory and concluded their disqualification proceedings without disqualification.

generally allowed the investigator to continue to function as an investigator, but imposed certain restrictions on his or her research, for example, by restricting the number of studies he or she may engage in at any time or the number of participants he or she may enroll in studies. Some consent agreements also required the investigator to obtain training in the conduct of clinical trials. Unlike disqualification that results from a Commissioner's decision, the consent agreements that specified restrictions generally applied to all FDA-regulated investigational products (not just drugs and biologics or devices) and were generally not permanent. In addition, some consent agreements specified restrictions on the individual's activities as a sub-investigator—activities that are not restricted if disqualification results from a Commissioner's decision.

- One consent agreement disqualified an investigator from receiving drugs and biologics, but not other FDA-regulated investigational products. This consent agreement did not specify any other restrictions on the investigator's activities.

Conclusions

To strengthen FDA's oversight of clinical investigators, FDA needs to ensure the timely completion of its debarments and disqualifications. Timely completion of these proceedings is critical to ensuring that individuals who have engaged in misconduct are prohibited from repeating the misconduct—that is, the actions that compromised the quality or integrity of clinical trial data or jeopardized the safety of clinical trial participants—and that individuals whose explanations FDA finds to be satisfactory can have their proceedings concluded quickly. While FDA's recent changes in policies and organization of responsibilities could improve the timeliness of debarment and disqualification proceedings, it is too soon to tell whether these efforts will be effective. For example, implementing the new time frames that FDA has established for debarment and disqualification could be challenging because some of these time frames are substantially shorter than the times FDA actually took in the proceedings we reviewed. Given the agency's competing priorities, it remains to be seen whether FDA will dedicate sufficient resources to debarment or disqualification proceedings to meet the time frames.

FDA's authority to debar or disqualify clinical investigators is an important component of its oversight of clinical investigators, specifically its efforts to protect human subjects and ensure the integrity of the data upon which it relies when evaluating new drugs, biologics, or devices for the U.S. market. It is critical for FDA to take action—and to have the authority to

take action—to prevent clinical investigators, sub-investigators, and study coordinators who engaged in serious misconduct from doing so again, whether in research that involves drugs, biologics, or devices. FDA’s current debarment authority does not fully extend to involvement with medical devices or prevent those who engaged in misconduct involving drugs or biologics from involvement with medical devices. In addition, FDA’s disqualification regulations limit a disqualification by a Commissioner’s decision to either investigational drugs and biologics or to investigational devices, thereby allowing an individual disqualified for misconduct related to drugs or biologics to receive investigational devices and vice versa. Moreover, a clinical investigator who is disqualified by a Commissioner’s decision is still able to serve as a clinical investigator for other FDA-regulated investigational products. As a result, FDA’s oversight of clinical investigators is limited.

Recommendations for Executive Action

We recommend that the Commissioner of FDA take the necessary steps to complete the following three actions:

- Pursue debarment authority for medical devices that is consistent with the current debarment authority for drugs and biologics and prohibit any debarred individual from involvement with drugs, biologics, and medical devices.
- Amend FDA regulations to ensure that those who have engaged in misconduct found sufficiently serious to warrant disqualification for one investigational medical product are not able to continue to serve as clinical investigators for any.
- Monitor compliance with recently established time frames for debarment and disqualification proceedings and take appropriate action when those are not met.

Agency Comments

We provided a draft of this report to the Department of Health and Human Services for review. The department provided written comments from FDA. In its comments, FDA agreed with our recommendations. FDA’s comments are reprinted in appendix VII. FDA also provided technical comments and updated information, which we incorporated as appropriate.

In its comments, FDA stated that the agency will endeavor to incorporate our recommendations into the agency's procedures. FDA agreed that providing the agency with the debarment authority to prohibit those who were convicted of certain crimes or otherwise involved in criminal activity from being involved in the medical device industry would benefit the development and approval process for medical devices. FDA also agreed that if a clinical investigator is disqualified from participating in clinical trials involving one type of investigational medical product, it is generally appropriate that the investigator be prohibited from participating in investigations of any FDA-regulated product. FDA stated that the agency intends to pursue revision of its regulations concerning clinical investigator disqualification to address this issue. In addition, FDA agreed that monitoring its success in meeting the recently established time frames for debarment and disqualification will be important as the agency strives to improve the timeliness of the debarment and disqualification processes, and it summarized steps it has already taken to do so.

As agreed with your offices, 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 to the Secretary of Health and Human Services, the Commissioner of FDA, relevant congressional committees, and interested parties. In addition, this report will be available at no charge on the GAO Web site at <http://www.gao.gov>.

If you or your staff have any questions concerning 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 VIII.



Marcia Crosse
Director, Health Care

Appendix I: Scope and Methodology

In this report, we examined the Food and Drug Administration's (FDA) time frames for debarment and disqualification proceedings, as well as limitations to the agency's statutory and regulatory authority related to these proceedings prior to November 2008. Until June 2008, other than the statutory requirement that debarment actions be initiated within 5 years of the date of the individual's conviction, FDA did not have criteria establishing time frames for the various steps it must take in debarment or disqualification proceedings. During the course of our work, three actions occurred that changed FDA's procedures for debarment and disqualification of clinical investigators.

- In June 2008, FDA issued a staff manual guide that, among other provisions, established time frames for the steps it must take after offering the clinical investigator an opportunity for a regulatory hearing in a disqualification proceeding.
- In January 2009, FDA issued a revised regulatory procedures manual that, among other provisions, established time frames for the steps it must take in disqualification proceedings prior to and through offering the clinical investigator an opportunity for a regulatory hearing.
- In March 2009, FDA issued a staff manual guide that, among other provisions, established time frames for the steps it must take in debarment proceedings.

At the time of our review, it was too soon to assess the effect of the changes in FDA's procedures and guidance on debarment and disqualification proceedings. Consequently, this report focuses on FDA's procedures as documented in proceedings that generally took place prior to issuance of the new time frames. We compare some of the times taken for the debarment and disqualification proceedings we reviewed with the new time frames.

To address our objectives, we reviewed FDA's debarment and disqualification files, interviewed FDA officials involved in debarment and disqualification proceedings, reviewed relevant laws, regulations, and FDA guidance, and reviewed standards for internal control. We conducted our file review from September 9, 2008, through November 5, 2008.

To determine how long FDA's debarment proceedings have taken and identify factors that contributed to the time frame for debarment, we reviewed FDA's files regarding all clinical investigators, sub-investigators, and study coordinators involved in research on drugs or biologics

intended for human use whom FDA pursued or considered pursuing for debarment from the time that it was given authority to do so on May 13, 1992, through September 9, 2008.¹ To identify these individuals, we reviewed information about FDA's debarment proceedings from *Federal Register* notices (including proposal to debar letters and final debarment orders) and FDA's Web site, and we confirmed whether or not these individuals were clinical investigators, sub-investigators, or study coordinators with FDA officials. We compared the information about debarment proceedings from FDA's Web site to the information in FDA's files and sought clarification when there were discrepancies.² We identified 18 completed or pending debarment proceedings pursued by FDA from May 13, 1992, through September 9, 2008—13 involving clinical investigators and 5 involving study coordinators.³

For each of these 18 debarment proceedings, we reviewed relevant files in the FDA center that initiated the debarment action—either the Center for Drug Evaluation and Research (CDER) or the Center for Biologics Evaluation and Research (CBER)—and in FDA's Division of Dockets Management, which maintains publicly available information about

¹Clinical investigators agree with the sponsor of an investigational product to take responsibility for the conduct of a particular study at one or more locations. Sub-investigators work under the supervision of clinical investigators. Study coordinators work for the investigators and typically interact directly with clinical trial participants. We included sub-investigators and study coordinators because, like clinical investigators, they interact directly with clinical trial participants. Individuals in any of these roles may be debarred for certain misconduct related to the development, approval, or regulation of any drug or biologic.

²For example, we found that FDA's Web site did not spell the name of one debarred individual as it was spelled in *Federal Register* notices. After we inquired about the discrepancy, FDA corrected the spelling on its Web site.

³We defined a debarment proceeding as pending if, as of the last date of our file review (Nov. 5, 2008), FDA had issued a proposal to debar letter, but had not completed the debarment proceeding, or if FDA had identified an individual as one whose conviction could serve as a basis for debarment, but for whom FDA had not issued a proposal to debar letter. Of the 18 completed or pending proceedings we identified, one of the study coordinators was also a sub-investigator.

debarment proceedings.⁴ We reviewed the documentation in the files to identify the date of each action in the debarment proceeding, along with information about who was involved and what occurred. We determined that the information we collected during our file review was sufficiently reliable for our purposes. After reviewing these files, we obtained additional information from FDA officials about proceedings in which the documentation we reviewed was incomplete. We also asked FDA officials to explain what, if anything, had occurred during any time intervals for which our review of the files indicated that 270 calendar days or more had passed without documented activity. We also followed up on proceedings that were pending as of the last day of our file review and on proceedings for which FDA's files on disqualification proceedings included information pertinent to a debarment proceeding.

To determine the time each completed debarment proceeding took, we calculated the number of calendar days from the date of the individual's conviction (or, for two proceedings in which the individual's conviction occurred before FDA received debarment authority, from the date when FDA received debarment authority—May 13, 1992) through completion of the debarment proceeding (i.e., the date of publication of a debarment order in the *Federal Register*). If the proceeding was pending, we calculated the number of calendar days through the last day of our file review. We also calculated the number of days during certain intervals in debarment proceedings, for example, from conviction to the issuance of a proposal to debar letter. To identify factors that contributed to the length of time FDA's debarment proceedings have taken, we analyzed the information we obtained from FDA's files and the additional information we obtained from FDA officials. We examined laws, regulations, and guidance to determine whether there were criteria relevant to the times taken by debarment proceedings and we interviewed FDA officials, including officials in CDER, CBER, the Office of Enforcement, and those involved with FDA's Debarment Working Group.

⁴In addition to the 18 debarment proceedings we identified, CDER also identified two individuals—a clinical investigator and a sub-investigator—who were convicted of relevant crimes, but who died while FDA was considering debarment. In addition, CDER officials told us that they did not debar one other clinical investigator who was convicted of a relevant crime because the staff responsible for debarments did not learn about the clinical investigator's conviction until more than 5 years after the conviction and the law governing debarment specifies that FDA must initiate debarment proceedings within 5 years of the date of conviction. We did not include these three additional proceedings in our analyses.

To determine how long FDA's disqualification proceedings have taken and identify factors that contributed to the time frame for disqualification, we reviewed FDA's files regarding all clinical investigators involved in research on drugs, biologics, or medical devices intended for human use for whom FDA pursued disqualification by issuing a Notice of Initiation of Disqualification Proceedings and Opportunity to Explain (NIDPOE) letter from January 1, 1998, through September 9, 2008, whether these clinical investigators were ultimately disqualified or not.⁵ To identify these individuals, we reviewed information about FDA's disqualification proceedings from FDA's Web site and obtained additional information from FDA about individuals for whom FDA pursued disqualification. We compared the information about disqualification proceedings from FDA's Web site to the information in FDA's files and sought clarification when there were discrepancies.⁶ We identified 52 completed and pending disqualification proceedings that FDA initiated by issuing a NIDPOE letter from January 1, 1998, through September 9, 2008.⁷

For each of these 52 disqualification proceedings, we reviewed relevant files in the FDA center that initiated the disqualification proceeding—CDER, CBER, or the Center for Devices and Radiological Health (CDRH)—as well as in other FDA offices that maintained files relating to these disqualification proceedings. These other offices included the Office of Enforcement, which is involved in the issuance of, and coordination of responses to, notice of opportunity for hearing (NOOH) letters; the Office

⁵According to FDA officials, the agency typically initiated disqualification proceedings before 1998 without issuing a NIDPOE letter.

⁶For example, we found that FDA's Web site did not accurately list the date on which 11 clinical investigators were disqualified. After we inquired about the discrepancies, FDA corrected the dates on its Web site.

⁷In addition to disqualification proceedings initiated with a NIDPOE letter, clinical investigators may be disqualified or restricted through agreements negotiated with the Department of Justice or by entering a consent agreement with FDA after an inspection, but without issuance of a NIDPOE letter. In addition to the 52 disqualification proceedings initiated with a NIDPOE letter that we included in our review, we identified 10 proceedings in which clinical investigators were disqualified or restricted from January 1, 1998, through September 9, 2008, without issuance of a NIDPOE letter (four through consent agreements with FDA that were entered without issuance of a NIDPOE letter, four through plea agreements, and two through settlement agreements negotiated with the Department of Justice on behalf of the FDA and other components of the Department of Health and Human Services). In addition, we identified one NIDPOE letter, issued on February 24, 2003, that was sent to an investigator who died after the inspection upon which the allegations in the NIDPOE letter were based, but before issuance of the NIDPOE letter. We did not include these additional proceedings in our analyses.

of the Ombudsman, which was responsible for regulatory hearings held as part of disqualification proceedings prior to spring of 2008; and the Good Clinical Practice Program,⁸ which began assuming responsibility for disqualification proceedings in spring of 2008 and hired a staff member to help oversee and monitor the disqualification process in June 2008. We reviewed the documentation in the files to identify the date of each action in the disqualification proceeding, along with information about who was involved and what occurred. We determined that the information we collected during our file review was sufficiently reliable for our purposes. After reviewing these files, we obtained additional information from FDA officials about proceedings in which the documentation we reviewed was incomplete. We also asked FDA officials to explain what, if anything, had occurred during any time intervals for which our review of the files indicated that 1 year or more had passed without documented activity. We also followed up on proceedings that were pending as of the last day of our file review.

To determine the time each completed disqualification proceeding took, we calculated the number of calendar days from the date of issuance of the NIDPOE letter through the conclusion of the disqualification proceeding (i.e., the date of issuance of a notice of disqualification, the date a consent agreement was signed by FDA, the date that FDA concluded the disqualification proceeding without disqualifying the investigator, or the date of a settlement agreement that concluded the disqualification proceeding).⁹ If the proceeding was pending, we calculated the number of calendar days through the last day of our file review. We also calculated the number of calendar days during certain

⁸In August 2009, the Good Clinical Practice Program was renamed the Office of Good Clinical Practice.

⁹For one proceeding in which FDA reissued the NIDPOE letter because the initial address was no longer correct, we used the initial issuance date for our calculations because that is the date FDA cited in the consent agreement that concluded the proceeding. For another proceeding, the investigator was prohibited from receiving investigational drugs, biologics, devices, and other FDA-regulated products as part of a plea agreement in a criminal proceeding. This investigator entered the plea agreement after an FDA hearing had begun and FDA continued the disqualification proceeding. FDA officials told us that they concluded that the terms of the plea agreement would not be enforceable after about 3 years. The presiding officer recommended disqualification, and the investigator requested a Commissioner's review. About 5 years after the investigator requested a Commissioner's review—9.5 years after issuance of the NIDPOE letter—FDA completed this disqualification proceeding with a Commissioner's decision to disqualify the investigator. We calculated the length of time this disqualification proceeding took from issuance of the NIDPOE letter to the date of the Commissioner's disqualification decision.

intervals in disqualification proceedings, for example, from a center's recommendation to issue a NOOH letter through issuance of that letter. To identify factors that contributed to the length of time FDA's disqualification proceedings have taken, we analyzed the information we obtained from FDA's files and the additional information we obtained from FDA officials. To determine whether the times taken for disqualification proceedings changed during the years covered in our review, we divided these proceedings into three groups based on the date when FDA issued the NIDPOE letter—those issued before 2002, those issued in 2002 through 2005, and those issued after 2005. We examined laws, regulations, and guidance to determine whether there were criteria relevant to the times taken by disqualification proceedings and we interviewed FDA officials.

To identify statutory and regulatory limitations of debarment and disqualification, we reviewed relevant laws, regulations, and guidance; reviewed files documenting FDA's debarment and disqualification proceedings; and interviewed FDA officials involved with debarment and disqualification proceedings.

We conducted this performance audit from June 2008 to September 2009, 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.

Appendix II: Selected Features of Debarment and Disqualification

	Debarment ^a	Disqualification
Authority	Pub. L. No.102-282, § 2 (21 U.S.C. § 335a)	21 C.F.R. §§ 312.2(a), 312.70 (2008) (drugs and biologics) 21 C.F.R. § 812.119 (2008) (devices)
Individuals to whom the action may be applied	<p>Individuals—including clinical investigators, sub-investigators, study coordinators, sponsors, and others—convicted of certain crimes or engaged in certain conduct. Debarment may be mandatory or permissive.</p> <p><i>Mandatory debarment:</i></p> <ul style="list-style-type: none"> For individuals convicted of a felony under federal law for conduct relating to the development, approval, or regulation of a drug product.^b <p><i>Permissive debarment:</i></p> <ul style="list-style-type: none"> For individuals convicted of a misdemeanor under federal law or a felony under state law for conduct relating to the development, approval, or regulation of a drug or biologic, or convicted of a conspiracy to commit, aid, or abet such crimes or a felony for which debarment is mandatory, if the type of conduct undermines the regulatory process for drugs or biologics, For individuals convicted of a felony for certain crimes or a conspiracy to commit, aid, or abet such a felony, if FDA finds that the individual has demonstrated a pattern of conduct sufficient to find there is reason to believe the individual may violate requirements related to drugs or biologics, or For individuals who materially participated in acts that were the basis for a different individual’s conviction for certain crimes, if FDA finds that the individual has demonstrated a pattern of conduct sufficient to find there is reason to believe the individual may violate requirements related to drugs or biologics.^c 	<p>Clinical investigators who have repeatedly or deliberately failed to comply with applicable FDA regulations or have repeatedly or deliberately submitted false information to FDA or the sponsor of the clinical trial in any required report.</p>
Examples of convictions or misconduct upon which the action could be based	<ul style="list-style-type: none"> Mail fraud (e.g., for submitting fraudulent data through the mail based on nonexistent clinical trial participants). Making false statements (e.g., by providing a false and fraudulent medical license to qualify as a clinical investigator). 	<ul style="list-style-type: none"> Repeatedly and deliberately failing to comply with FDA regulations requiring informed consent of clinical trial participants (e.g., by failing to advise them of the risks of participation). Deliberately submitting false data to the sponsor of a clinical trial (e.g., submitting fraudulent data based on nonexistent clinical trial participants) in a required report.

Appendix II: Selected Features of Debarment and Disqualification

	Debarment^a	Disqualification
Consequences of the action for the individual	No longer permitted to provide services in any capacity to an individual, corporation, partnership, or association that has an approved or pending drug or biologic application. If such services are provided, civil monetary penalties may be assessed. ^d	<p>If disqualified by a Commissioner’s decision:</p> <ul style="list-style-type: none"> No longer entitled to receive FDA-regulated investigational drugs and biologics or FDA-regulated investigational devices and therefore unable to serve as a clinical investigator for the type of product (i.e., drugs and biologics or devices) for which the action was taken. <p>If disqualified by consent agreement:</p> <ul style="list-style-type: none"> Terms of agreement may be subject to negotiation, which could result in disqualification from receiving some or all FDA-regulated investigational products, or restrictions such as limits on the number of clinical studies the investigator may conduct and requiring that the investigator be supervised by another clinical investigator.
Duration	<p><i>Mandatory:</i> Permanent.</p> <p><i>Permissive:</i> Up to five years for each offense.^e</p>	Disqualification is permanent unless otherwise specified in a consent agreement or the investigator is reinstated. ^f
Time frame for initiation of action	Must occur within 5 years of conviction or the date of the action on which debarment is based. ^g	No limit.

Source: GAO.

^aThe selected features of debarment presented in this table relate to individuals (including clinical investigators, sub-investigators, and study coordinators) who may be debarred from involvement with drugs and biologics, and not to corporations, partnerships, or associations.

^bThe statutory definition of “drug product” includes drugs and biologics. 21 U.S.C. § 321(dd).

^cIndividuals may also be permissively debarred if they are high managerial agents who worked for, or who worked as a consultant for, an individual convicted of a felony resulting in debarment, and who had knowledge of such activity and knew it was a violation, but did not report it, and if FDA determines that the type of conduct which served as the basis for such other individual’s conviction undermines the process for the regulation of drugs or biologics. High managerial agents are officers or directors of a corporation or an association, partners of a partnership, or any employee or other agent of a corporation, association, or partnership having duties such that their conduct may fairly be assumed to represent the policy of the corporation, association, or partnership, and includes persons having management responsibility for submissions to the FDA regarding the development or approval of any drug product; production, quality assurance, or quality control of any drug product; or research and development of any drug product. 21 U.S.C. §§ 321(cc), 335a(b)(2)(B)(iv).

^d21 U.S.C. § 335b(a)(7).

^eIf the individual is permissively debarred for multiple offenses, the Commissioner may determine whether debarment periods will run concurrently or consecutively. FDA is required to terminate an individual’s debarment if, for example, the conviction that served as the basis for the individual’s debarment is reversed. 21 U.S.C. §§ 335a(c)(2)(A), (d)(3)(B)(i).

^fClinical investigators who have been disqualified may apply to be reinstated as eligible to receive investigational products. Reinstatement requires a Commissioner’s determination that the investigator has presented adequate assurances that the investigator will employ investigational products in compliance with FDA regulations. 21 C.F.R. §§ 312.70(f), 812.119(f) (2008).

^g21 U.S.C. § 335a(l)(2).

Appendix III: Debarment Proceedings Completed or Pending from May 13, 1992, through September 9, 2008

Proceeding	Individual's role	Center involved in proceeding ^a	Type of debarment proposed ^b	Date of conviction	Date of issuance of proposal to debar ^c	Date of debarment order ^d
Kostas, Constantine I.	clinical investigator	CDER	mandatory	10/13/1988 ^e	12/9/1992	6/25/1998
Fogari, Robert A.	clinical investigator	CDER	mandatory	2/2/1989 ^e	1/4/1993	7/8/1993
Garfinkel, Barry D.	clinical investigator	CDER	mandatory	11/19/1993	1/27/1995	4/2/1997
Fiddes, Robert A.	clinical investigator	CDER	permissive	9/30/1997	5/31/2002	11/6/2002
Charpentier, Laverne M.	study coordinator	CDER	permissive	10/21/1997	5/6/2002	12/2/2002
Rescinded ^f	study coordinator	CDER	permissive	10/22/1997	5/6/2002	11/6/2002
Pending A	clinical investigator	CDER	permissive	12/16/1997	11/26/2002	pending ^g
Borison, Richard L.	clinical investigator	CDER	permissive	10/8/1998	11/26/2002	9/30/2003
Peugeot, Renee	sub-investigator and study coordinator	CDER	mandatory	3/23/2000	4/29/2002	1/13/2003
Caro Acevedo, Eduardo	clinical investigator	CDER	permissive	2/16/2001	2/18/2004	3/24/2005
Pending B	clinical investigator	CDER	permissive	10/28/2002	10/10/2007	pending ^h
Pending C	clinical investigator	CDER	debarment had not been proposed ⁱ	12/11/2003	pending ⁱ	pending ⁱ
Campbell, Maria Anne Kirkman ^j	clinical investigator	CDER	mandatory	3/25/2004	2/28/2007	9/2/2008
Butkovitz, Anne L.	study coordinator	CBER	mandatory	6/7/2005	2/21/2006	10/17/2006
Pending D	clinical investigator	CBER	mandatory	8/4/2005	9/7/2007	pending ^k
Pending E	study coordinator	CDER	debarment had not been proposed ⁱ	12/6/2005	pending ⁱ	pending ⁱ
Pending F	clinical investigator	CDER	debarment had not been proposed ^m	4/24/2007	pending ^m	pending ^m
Pending G	clinical investigator	CDER	debarment had not been proposed ⁱ	9/11/2007	pending ⁱ	pending ⁱ

Source: GAO analysis of data from FDA.

Note: This table shows all completed or pending debarment proceedings initiated from May 13, 1992, through September 9, 2008, against clinical investigators, sub-investigators, and study coordinators involved in research on drugs or biologics intended for human use. The names of individuals who have been debarred are public information: Debarments are published in the *Federal Register* and FDA posts the names of debarred individuals on its Web site. We defined a debarment proceeding as initiated if FDA identified the individual as one whose conviction could serve as a basis for debarment. We defined a debarment proceeding as pending if, as of the last date of our file review (Nov. 5, 2008), FDA had issued a proposal to debar letter, but had not concluded the debarment proceeding, or if FDA had identified an individual as one whose conviction could serve as a basis for debarment, but for whom FDA had not issued a proposal to debar letter. In addition to the individuals in the proceedings above, CDER identified a clinical investigator and a sub-investigator who were convicted of relevant crimes, but who died while FDA was considering debarment. In addition, CDER identified a clinical investigator who was convicted of a relevant crime, but who was not debarred because CDER learned about the clinical investigator's conviction more than 5 years after the conviction. The law governing debarment specifies that FDA must initiate debarment actions within 5 years of the date of conviction. These proceedings are not included.

**Appendix III: Debarment Proceedings
Completed or Pending from May 13, 1992,
through September 9, 2008**

^aThe FDA centers that pursued debarment of individuals in our review included CDER and CBER.

^bThere are two types of debarment: mandatory and permissive. Debarment is mandatory—and permanent—when FDA finds that an individual has been convicted of a felony under federal law for conduct relating to the development or approval of any drug or biologic, or otherwise relating to the regulation of any drug or biologic. FDA may seek permissive debarment—which is not permanent—under certain other conditions, for example, if the individual was convicted of a felony under state law related to the development, approval, or regulation of drugs or biologics. To seek permissive debarment, FDA must determine that debarment is appropriate and determine the period of debarment by considering factors such as the nature and seriousness of the offense or offenses involved. An individual may be permissively debarred for up to 5 years for each offense.

^cFDA issues a proposal to debar letter to initiate a debarment proceeding. This letter describes the conviction and actions of relevance to the proceeding, offers the investigator the opportunity for a formal hearing, and specifies the time period within which the investigator must provide a written request for a hearing.

^dWe defined a debarment proceeding as completed as of the date on which FDA published a debarment order in the *Federal Register*.

^eThe individual in this debarment proceeding was convicted prior to May 13, 1992, the date on which FDA obtained the authority to debar. The law governing debarment allows FDA to pursue debarment for individuals who were convicted prior to May 13, 1992.

^fFDA rescinded the debarment order in January 2003 after the agency learned that it had sent the proposal to debar letter to another person with the same name as the individual involved in this proceeding. When FDA learned that the proposal to debar letter had been sent to the wrong person, just over 5 years had elapsed from the date of the study coordinator's conviction.

^gThis debarment proceeding remained pending as of September 1, 2009.

^hThis debarment proceeding was pending as of November 5, 2008, which was the last date of our file review, but FDA issued a debarment order on June 12, 2009.

ⁱFDA had not proposed debarment as of November 5, 2008, which was the last date of our file review, but FDA issued a proposal to debar letter for mandatory debarment on November 25, 2008, and a debarment order on June 12, 2009.

^jThis investigator is also known as Maria Anne Campbell.

^kThis debarment proceeding was pending as of November 5, 2008, which was the last date of our file review, but FDA issued a debarment order on November 24, 2008.

^lFDA had not proposed debarment as of November 5, 2008, which was the last date of our file review, but FDA issued a proposal to debar letter for mandatory debarment on May 4, 2009, and a debarment order on August 4, 2009.

^mFDA had not proposed debarment as of November 5, 2008, which was the last date of our file review, but FDA issued a proposal to debar letter for permissive debarment on June 2, 2009. This debarment proceeding remained pending as of September 1, 2009.

Appendix IV: Types of Misconduct Cited in Proposal to Debar Letters

Proceeding	Misconduct related to:					Specific example of misconduct
	Falsifying study participant data	Diverting funds for own financial gain	Bribing staff to conceal information	Illegally prescribing or allowing the illegal prescription of medication	Conspiring to defraud government	
Borison, Richard L.		X	X	X		Defrauded employer of more than \$10 million in clinical research funds by diverting funds to entities owned or controlled by the clinical investigators.
Butkovitz, Anne L.	X					Documented that study participants were contacted and that no serious adverse experiences had occurred when, in fact, such contacts were not made.
Campbell, Maria Anne Kirkman ^a	X					Submitted falsified data for a nonexistent study participant.
Caro Acevedo, Eduardo					X	Received kickbacks in relation to the referral of Medicare beneficiaries to a durable medical equipment company, in violation of the Medicare anti-kickback law.
Charpentier, Laverne M.	X					Substituted samples and data from qualifying subjects for nonqualifying subjects.
Fiddes, Robert A.	X					Falsely reported that certain subjects participated in clinical studies when, in fact, they had not.
Fogari, Robert A.	X					Falsified X-ray and physical exam results to show that the drug was effective.
Garfinkel, Barry D.	X					Submitted data indicating that subject visits were conducted when, in fact, they were not.
Kostas, Constantine I.	X					Submitted data for 70 fictitious study participants.
Peugeot, Renee	X					Manipulated test results in clinical studies.

Source: GAO analysis of data from FDA.

**Appendix IV: Types of Misconduct Cited in
Proposal to Debar Letters**

Notes: A proposal to debar letter details the misconduct that led to an individual's conviction. The proposal to debar letters covered in this table include those that FDA issued after receiving authority to debar on May 13, 1992, through September 9, 2008, for clinical investigators, sub-investigators, and study coordinators whose debarment proceedings were completed (and not rescinded) as of November 5, 2008 (the last date of our file review). The names of individuals who have been debarred are public information: Debarments are published in the *Federal Register* and FDA posts the names of debarred individuals on its Web site.

^aThis investigator is also known as Maria Anne Campbell.

Appendix V: Disqualification Proceedings Initiated from January 1, 1998, through September 9, 2008

Proceeding	FDA Center ^a	Dates of Inspections	Date of issuance of NIDPOE letter ^b	Date of issuance of NOOH letter ^c	Date of outcome	Outcome			Basis for outcome			
						Disqualified to receive drugs and biologics	Disqualified to receive devices	Restricted ^d	Neither disqualified nor restricted	FDA decision ^e	Consent agreement	Settlement agreement
1	CDER	6/20-24/1996; 5/19-23/1997	3/23/1998	4/15/1999	6/18/2008	X				X		
2	CDER	3/11-13/1998	7/1/1998	N/A	8/11/1999			X			X	
3	CDER	3/9-10/1998	7/1/1998	N/A	9/10/1999			X ^f			X	
4	CDER	6/10/1997- 10/9/1997	7/10/1998	6/28/1999	9/1/1999			X ^f			X	
5	CDER	5/7/1997- 7/22/1997	8/28/1998	8/18/1999	7/30/2002	X				X		
6 ^g	CDER	4/12/1995- 5/16/1995	11/6/1998	8/16/1999	5/20/2008	X				X		
7	CDER	7/6-16/1998	12/23/1998	N/A	3/30/1999				X	X		
8	CDER	2/5/1998- 3/12/1998	5/19/1999	2/19/2000	1/12/2004			X ^f			X	
9	CBER	12/7-9/1999	4/6/2000	1/8/2002	4/4/2003	X	X				X	
10	CDER	10/5/1999- 11/11/1999	4/7/2000	N/A	6/19/2002			X ^f			X	
11	CBER	7/12/1999- 9/15/1999	6/30/2000 ^h	11/1/2002	10/23/2006	X				X		
12	CDER	11/22/1999- 3/15/2000	8/21/2000	N/A	8/23/2002			X ^f			X	
13	CDER	4/12/1999- 8/4/1999; 2/27/2001- 3/8/2001	9/13/2000 ⁱ	N/A	1/10/2005	X	X				X	
14	CBER	11/30/1999- 1/19/2000	11/30/2000	2/8/2002	2/9/2005			X				X
15	CDER	5/30/2000- 6/27/2000	4/13/2001	11/28/2003	2/5/2004	X	X				X	
16	CDRH	3/14/2001- 4/18/2001	5/11/2001	1/8/2002	6/18/2002		X			X		
17	CBER	7/17/2000- 8/4/2000	6/21/2001	5/21/2002	pending ^j							
18	CDER	5/30/2000- 6/27/2000	6/27/2001	6/3/2002	9/24/2003	X				X		
19	CDER	8/14-23/2001	6/27/2002	N/A	12/12/2002	X	X				X	
20	CDER	5/12/1998- 7/21/1998	10/23/2002	N/A	8/11/2003			X ^f			X	

**Appendix V: Disqualification Proceedings
Initiated from January 1, 1998, through
September 9, 2008**

Proceeding	FDA Center ^a	Dates of Inspections	Date of issuance of NIDPOE letter ^b	Date of issuance of NOOH letter ^c	Date of outcome	Outcome			Basis for outcome			
						Disqualified to receive drugs and biologics	Disqualified to receive devices	Restricted ^d	Neither disqualified nor restricted	FDA decision ^e	Consent agreement	Settlement agreement
21	CBER	8/22/2001-11/16/2001	11/6/2002	10/9/2003	1/9/2007			X			X	
22	CBER	7/19/2002-9/6/2002	6/23/2003	2/4/2004	3/14/2008	X				X		
23	CDER	7/23/2001-8/28/2001	12/3/2003	N/A	pending ^k							
24	CDRH	5/2-21/2003	3/9/2004	N/A	2/8/2005			X			X	
25	CDRH	6/2-6/2003	3/11/2004	N/A	2/8/2005			X			X	
26	CBER	4/1-18/2003	4/22/2004	N/A	10/3/2004	X	X				X	
27	CDRH	4/11/2003-5/13/2003	5/5/2004	N/A	4/10/2005			X			X	
28	CDER	2/19/2002-4/3/2002	6/10/2004	3/8/2006	5/11/2006			X			X	
29	CDER	2/26/2002-3/29/2002; 1/27/2003-2/14/2003	6/8/2004 ^l	N/A	11/28/2005			X			X	
30	CDER	6/1-22/2000	8/17/2004	N/A	1/14/2005			X ^j			X	
31	CDER	11/14/2002-1/03/2003	9/22/2004	8/14/2007	8/25/2008	X				X		
32	CDRH	7/29/2002-8/9/2002; 12/3-12/2002; 1/27/2003-2/6/2003	9/30/2004	N/A	4/15/2005			X ^j			X	
33	CDER	10/21-25/2002	1/19/2005	N/A	6/23/2008			X			X	
34	CDER	3/11-14/2002	3/1/2005	N/A	1/9/2006			X			X	
35	CDER	7/24/2003-8/6/2003	8/24/2005	N/A	9/29/2005	X	X				X	
36	CDRH	2/17/2004-3/23/2004; 3/30/2004-4/1/2004	10/21/2005	N/A	7/19/2006			X			X	
37	CDER	3/10/2003-4/3/2003	1/20/2006	N/A	10/11/2006	X	X				X	
38	CDER	3/4-10/2005	5/10/2006	N/A	2/21/2008	X	X				X	
39	CDER	7/29/2002-8/28/2002	5/11/2006	pending ^m	pending ^m							
40	CDER	10/15-24/2002	5/18/2006	12/21/2007	5/8/2008	X				X		

**Appendix V: Disqualification Proceedings
Initiated from January 1, 1998, through
September 9, 2008**

Proceeding	FDA Center ^a	Dates of Inspections	Date of issuance of NIDPOE letter ^b	Date of issuance of NOOH letter ^c	Date of outcome	Outcome			Basis for outcome			
						Disqualified to receive drugs and biologics	Disqualified to receive devices	Restricted ^d	Neither disqualified nor restricted	FDA decision ^e	Consent agreement	Settlement agreement
41	CBER	2/8-28/2005; 3/16/2005- 8/2/2005	1/24/2007	N/A	5/18/2007	X	X				X	
42	CDER	1/9-21/2004	5/9/2007	N/A	5/5/2008	X						X
43	CDRH	10/17-20/2006	7/31/2007	N/A	10/12/2007				X	X		
44	CDER	2/16/2005- 4/6/2005	8/15/2007	N/A	9/10/2007	X	X					X
45	CDER	8/25/2003- 9/3/2003	8/29/2007	N/A	4/24/2008	X	X					X
46	CDER	10/25/2006- 2/7/2007	9/27/2007	N/A	2/12/2008	X	X					X
47	CBER	6/16/2005- 7/22/2005	11/9/2007	N/A	4/28/2008	X	X					X
48	CDER	8/2/2004- 12/8/2004	1/24/2008	N/A	7/25/2008	X	X					X
49	CDER	5/17/2005- 6/7/2005	2/21/2008	N/A	8/25/2008			X				X
50	CDER	3/22/2007- 4/18/2007	3/31/2008	pending ⁿ	pending ⁿ							
51	CDER	1/22/2008- 2/25/2008	8/25/2008	N/A	9/22/2008	X	X					X
52	CBER	5/8-12/2006; 9/18-21/2006	8/27/2008	pending ^o	pending ^o							

Source: GAO analysis of data from FDA.

N/A = not applicable

Notes: This table shows all proceedings initiated by a NIDPOE letter from January 1, 1998, through September 9, 2008. We defined a disqualification proceeding as pending if, as of the last date of our file review (Nov. 5, 2008), FDA had issued a NIDPOE letter, but had not concluded the disqualification proceeding. One clinical investigator died after the inspection upon which the allegations in the NIDPOE letter were based, but before receiving the NIDPOE letter; this investigator's case is not included. Clinical investigators who were disqualified from receiving drugs and biologics and from receiving devices were also disqualified from receiving any FDA-regulated investigational products, including food additives and animal drugs.

^aThe FDA centers that pursued disqualification of clinical investigators in our review were CDER, CBER, and CDRH.

^bFDA issues a NIDPOE letter to initiate a disqualification proceeding. The NIDPOE letter details FDA's allegations of misconduct based on its findings during one or more inspections and offers the clinical investigator an opportunity to respond to the allegations in writing or in an informal conference.

^cFDA uses a NOOH letter to provide a clinical investigator an opportunity for a regulatory hearing as part of a disqualification proceeding.

**Appendix V: Disqualification Proceedings
Initiated from January 1, 1998, through
September 9, 2008**

^dWhen a clinical investigator was restricted, the clinical investigator agreed to certain restrictions on his or her research when entering a consent agreement with FDA or a settlement agreement negotiated with the Department of Justice.

^eFDA decisions include decisions by the Commissioner (or delegate) to disqualify a clinical investigator and decisions by the responsible center to neither disqualify nor restrict the clinical investigator, based on the center's finding that the investigator's explanation for all of the allegations in the NIDPOE letter was satisfactory.

^fThis disqualification proceeding was concluded when the clinical investigator and FDA entered a consent agreement that specified restrictions to the investigator's activities. The restrictions were subsequently removed because, under the terms of the consent agreement, they no longer applied.

^gThis investigator was prohibited from receiving investigational drugs, biologics, devices, and other FDA-regulated products as part of a plea agreement in a criminal proceeding. FDA continued the disqualification proceeding against this investigator after he entered the plea agreement. FDA officials told us that they concluded that the terms of the plea agreement would not be enforceable after about 3 years and they continued the disqualification proceeding.

^hFDA issued an amendment to the NIDPOE letter, which detailed additional allegations of misconduct, on August 17, 2001.

ⁱFDA issued an amendment to the NIDPOE letter, which detailed additional allegations of misconduct, on June 23, 2003.

^jThis disqualification proceeding was pending as of November 5, 2008, when we completed our review of files, but has since been concluded. This clinical investigator was disqualified from receiving investigational drugs and biologics through a Commissioner's decision on January 8, 2009.

^kThis disqualification proceeding remained pending as of September 1, 2009.

^lFDA re-issued this NIDPOE letter on July 20, 2004, after learning that the original address was not correct.

^mThis disqualification proceeding was pending as of November 5, 2008, which was the last date of our file review. This clinical investigator was issued a NOOH letter on July 1, 2009. This disqualification proceeding remained pending as of September 1, 2009.

ⁿThis disqualification proceeding was pending as of November 5, 2008, which was the last date of our file review, but has since been concluded. This clinical investigator was issued a NOOH letter on March 4, 2009, and was disqualified from receiving investigational drugs, biologics, devices, and other FDA-regulated investigational products, including food additives and animal drugs, through a consent agreement on May 4, 2009.

^oThis disqualification proceeding was pending as of November 5, 2008, which was the last date of our file review, but has since been concluded. This clinical investigator was issued a NOOH letter on February 13, 2009; the NOOH letter was re-issued on March 9, 2009, after the agency learned that the investigator had not received the letter. This clinical investigator was disqualified from receiving investigational drugs and biologics through a Commissioner's decision on August 6, 2009.

Appendix VI: Types of Alleged Misconduct Cited in FDA's Initiation of Disqualification Proceedings

Common types of alleged misconduct cited in NIDPOE letters issued by FDA from January 1, 1998, through September 9, 2008, included

- Submitting false information to the sponsor or to FDA;
- Failure to comply with requirements related to obtaining informed consent from clinical trial participants;
- Failure to comply with requirements to obtain initial or continuing approval from an institutional review board;
- Failure to follow the clinical trial's research plan;
- Failure to comply with requirements regarding the disposition of investigational drugs, biologics, or devices, such as maintaining records of their use; and
- Failure to comply with requirements to prepare or maintain case histories or other records.

Specific examples of the types of alleged misconduct detailed in the NIDPOE letters for the 45 completed proceedings that we reviewed that ended in disqualification (including restrictions) are shown in table 1.

**Appendix VI: Types of Alleged Misconduct
Cited in FDA's Initiation of Disqualification
Proceedings**

Table 1: Examples of Misconduct Allegations Cited in NIDPOE Letters

Letter	Specific example of alleged misconduct
1	Failed to maintain adequate and accurate case histories that recorded all observations and other data pertinent to a clinical trial of an investigational drug.
2	Failed to obtain approval from the institutional review board for a verbal informed consent procedure that was used with the participants in a clinical trial of an investigational drug.
3	Failed to maintain adequate and accurate records by inaccurately reporting that four clinical trial participants had been using a stable dose of a medication for a minimum of 7 days prior to their respective screening visit dates.
4	Enrolled 390 high-risk participants in a clinical trial of an investigational test kit, even though the protocol and conditions of approval by the institutional review board limited the number of enrolled high-risk participants to 200.
5	Failed to report to the institutional review board unanticipated adverse effects, including chronic and severe pain, experienced by several clinical trial participants after implantation of an investigational medical device.
6	Failed to evaluate adverse events in a timely manner or to take appropriate action to protect participants in clinical trials of an investigational drug who experienced adverse events, including failing to take appropriate actions to evaluate the adverse reactions reported by one clinical trial participant for more than 6 months.
7	Submitted false information in a required report to the sponsor of an investigational drug by submitting case report forms for over 200 clinical trial participants who had not, in fact, participated in the clinical trial.
8	Failed to report to the sponsor adverse events, including headache, fever, and palpitations, that were experienced by participants in clinical trials of an investigational drug intended for the treatment of ear infection.
9	Failed to maintain any records accounting for the use of investigational biologics in two clinical trials that involved 5 and 28 clinical trial participants, respectively.
10	Failed to institute corrective actions in response to repeated letters sent over a period of 11 months by the sponsors of investigational drugs concerning violations of the protocols for clinical trials, discrepancies in required documentation, and missing medical records.
11	Failed to document the occurrence and follow-up of serious adverse events (including hospitalizations) experienced by infant participants in a clinical trial of an investigational vaccine.
12	Submitted false information to the sponsor of an investigational drug by submitting data from sputum samples that did not come from the actual clinical trial participants.
13	Failed to recognize or evaluate adverse events in a timely manner and failed to take appropriate action to protect those who experienced adverse events, including continuing to provide an investigational drug to a clinical trial participant who experienced multiple signs and symptoms of myocardial injury and drug toxicity until one day before his death, about 3 weeks after he began participating in the clinical trial.
14	Failed to supervise the clinical trial of an investigational drug, allowing the study coordinator—who was not licensed as a physician in the state in which the trial occurred—to write medical orders that were not co-signed by a licensed physician.
15	Enrolled an individual with a duodenal ulcer (but no gastric ulcer) in a clinical trial of an investigational drug intended for use with patients with gastric ulcer, even though the protocol stated that only patients with a gastric ulcer were eligible to participate.
16	Failed to seek approval from the institutional review board for changing the protocol for a clinical trial of an investigational drug to allow enrollment of participants who, according to the approved protocol, should have been excluded from the clinical trial.
17	Failed to provide FDA with required information identifying sub-investigators.
18	Maintained two separate sets of medical records for clinical trial participants that covered the same time period, with one set of records (which were for his private practice) documenting that several participants had pre-existing conditions that should have precluded their enrollment in the study.

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Letter	Specific example of alleged misconduct
19	Stored an investigational drug that was a controlled substance in an unlocked cabinet, thereby failing to take adequate precautions to prevent diversion of the controlled substance into illegal channels of distribution.
20	Enrolled a clinical trial participant in a study for which he was ineligible because of impaired liver and renal function, gave the participant an investigational drug that likely contributed to his death, and altered laboratory results in the report to the sponsor to make it appear that the participant was eligible for enrollment.
21	Failed to report to the institutional review board unanticipated problems that involved risks to humans in a timely manner, including failing to report for nearly 2 years that a participant in a clinical trial of an investigational drug experienced acute renal failure.
22	Allowed participants enrolled in clinical trials of an investigational drug to continue taking medications that, according to the protocol, were prohibited during their participation.
23	Submitted false information to the sponsor of an investigational drug by submitting reports based on medical records for clinical trial participants that had been written more than one year after the events they ostensibly described.
24	Failed to meet a requirement of reporting the number of eyes treated by an investigational medical device to FDA.
25	Exported an investigational new drug to unauthorized personnel in other countries and charged or received payment from overseas contacts in return for the use of the investigational drug without seeking FDA's approval or authorization to export the investigational drug or to charge for it.
26	Delegated certain tasks associated with a clinical trial of an investigational vaccine, including performing physical examinations and post-vaccination observations, to individuals who were not qualified to perform them.
27	Failed to properly train and supervise sub-investigators and other staff involved in a clinical trial of an investigational biologic for infants, for example, by failing to inform an individual who administered the investigational biologic that he was to obtain information about serious adverse experiences.
28	Failed to submit blood samples taken from clinical trial participants to a laboratory for testing to evaluate the presence of clinically significant abnormal values as required by the protocols for two clinical trials of an investigational drug.
29	Failed to obtain informed consent from 30 participants prior to enrolling them in a clinical trial of an investigational drug and instructed a staff member to backdate informed consent documents for 8 of them.
30	Submitted false information to the sponsor of an investigational drug by fabricating all records associated with seven fictitious clinical trial participants, including forging consent forms, fabricating medical information, and knowingly and willingly submitting blood and urine samples, supposedly from these participants, but actually taken from surplus specimens from patients in his clinical practice.
31	Failed to report serious adverse events, including deaths, to an institutional review board until months after their occurrence, even though the institutional review board had specifically required immediate reporting of any unanticipated problems, injuries, or deaths.
32	Failed to obtain information about adverse events experienced by the participants in a clinical trial of an investigational drug, even though the protocol required collection of this information.
33	Administered an investigational new vaccine that was obtained by an unapproved process to three clinical trial participants—one of whom later died—without authorization to administer that drug to human participants.
34	Submitted false information to investigational drug sponsors and to the FDA by reporting that he had a Ph.D. degree or a family nurse practitioner degree when, in fact, he did not have valid degrees of either type.
35	Continued to include participants in a clinical trial of an investigational drug after documenting that they had reactions such as pain that, according to the protocol, should have led to termination of their participation.
36	Failed to ensure and document that all clinical trial participants were aware that a device was investigational prior to surgically implanting it.
37	Failed to supervise clinical trials, causing submission of false information (electrocardiograms that had been altered to appear to have been recorded at a different time than they actually were) to the sponsor of an investigational drug.

**Appendix VI: Types of Alleged Misconduct
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Letter	Specific example of alleged misconduct
38	Failed to obtain written informed consent from three participants in a clinical trial of an investigational drug and falsified their signatures on informed consent documents some time after their enrollment in the trial.
39	Gave participants in a clinical trial of an investigational drug amounts of the investigational drug that differed from those specified by the protocol.
40	Did not have or provide to FDA a complete list of the clinical trial participants in whom an investigational medical device had been implanted.
41	Delegated responsibilities that included screening and enrolling clinical trial participants to a study coordinator who lacked the medical training necessary to perform those functions and failed to supervise the study coordinator, resulting in enrollment of two participants who, for safety reasons, should have been excluded from the clinical trial of an investigational drug.
42	Failed to document that informed consent was obtained from all clinical trial participants and that all participants met the enrollment eligibility criteria for a clinical trial of an investigational device.
43	Failed to obtain approval of the protocol for a clinical trial of an investigational drug from the institutional review board before initiating it.
44	Submitted inaccurate and misleading reports to the institutional review board regarding the safety of a clinical trial of an investigational biologic.
45	Failed to maintain adequate and accurate case histories of participants in clinical trials of investigational drugs by making changes to records without documenting why or by whom these changes were made.

Source: GAO analysis of data from FDA.

Notes: A NIDPOE letter provides a clinical investigator with notice of initiation of a disqualification proceeding and details FDA's allegations of misconduct based on its findings during one or more inspections of the clinical investigator's conduct of one or more clinical trials. This letter offers the clinical investigator a chance to respond in writing or meet informally with FDA officials to discuss the alleged violations. FDA may determine not to pursue disqualification based on certain allegations cited in the NIDPOE letter after FDA's evaluation of the clinical investigator's response. The 45 NIDPOE letters covered in this table were issued by FDA from January 1, 1998, through September 9, 2008, for disqualification proceedings that ended in disqualification (including restrictions).

Appendix VII: 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

SEP 8 2009

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

Dear Ms. Crosse:

Enclosed are comments on the U.S. Government Accountability Office's (GAO) report entitled: OVERSIGHT OF CLINICAL INVESTIGATORS: Action Needed to Improve Timeliness and Enhance Scope of FDA's Debarment and Disqualification Processes for Medical Product Investigators (GAO-09-807)

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

Sincerely,

A handwritten signature in black ink, appearing to read "Andrea Palm".

Andrea Palm
Acting Assistant Secretary for Legislation

Enclosure

FDA's General Comments to the GAO Draft Report Entitled, Oversight of Clinical Investigators: Action Needed to Improve Timeliness and Enhance Scope of FDA's Debarment and Disqualification Processes for Medical Product Investigators (GAO-09-807)

The Food and Drug Administration (FDA or Agency) appreciates the opportunity to review and comment on the Government Accountability Office's (GAO) draft report. Clinical investigator disqualification and debarment are key remedial measures used by the Agency to protect the public health. Prohibiting certain individuals from being involved in the clinical trial process for medical products is critical to protecting research subjects and ensuring the integrity and reliability of data used to support Agency decision making. Disqualification and debarment matters are therefore a high priority for the Agency, and FDA has made strides over the last two years to improve the processes for both of these important administrative actions. The Agency appreciates GAO's recommendations for improvement and will endeavor to incorporate them into its new procedures.

In 2006, FDA launched its Human Subject Protection/Bioresearch Monitoring Initiative.¹ As part of this initiative, FDA is scrutinizing its oversight of clinical trials, including clinical investigator disqualification and debarment proceedings. As recently noted by the Agency² and discussed below, FDA has greatly improved its handling of these important remedial actions. FDA has also made the processes and final determinations more transparent to help ensure that individuals found to be non-compliant do not continue to be involved in new product development.

Clinical Investigator Disqualification

FDA's disqualification processes and associated time frames have improved considerably in the recent past. Over the last two years, the Agency has revamped its procedures and processes to provide uniformity, efficiency, and effective oversight of the Agency's handling of disqualification matters. Making the disqualification process more uniform throughout FDA and adding targeted time frames for the various steps in the process is facilitating timely resolution of disqualification actions. FDA has also engaged in a number of other activities to improve the clinical investigator disqualification process and protect the public health.

Procedures

Recognizing that recommended time frames and identified staff would strengthen its ability to conclude disqualification actions more efficiently, FDA created new procedures and updated existing ones. FDA revised its Regulatory Procedures Manual (RPM), Chapter 5, to include a new section (5-9) – "Disqualification of Clinical Investigators".³ This new section identifies responsibilities and time frames from the clinical investigator site inspection (found to have serious noncompliance) through issuance of the notice of opportunity for a hearing.

¹ See www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2006/ucm108677.htm. FDA issued an update on this initiative in March 2009. See www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/ucm134452.htm.

² See www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm176040.htm.

³ See www.fda.gov/downloads/ICECI/ComplianceManuals/RegulatoryProceduresManual/UCM074324.pdf; updated chapter effective December 2008.

FDA's General Comments to the GAO Draft Report Entitled, Oversight of Clinical Investigators: Action Needed to Improve Timeliness and Enhance Scope of FDA's Debarment and Disqualification Processes for Medical Product Investigators (GAO-09-807)

FDA also revised the compliance program chapter for clinical investigators⁴ to include a listing of sanctions available to FDA and examples of violations that may warrant an official action indicated (OAI) classification. As requested by the Office of the Inspector General, this document defines threshold criteria for issuing warning letters and for initiating disqualification actions and contains recommendations for enhanced communication between headquarters and field staff.

FDA finalized Staff Manual Guide 7711 – “Disqualification of a Clinical Investigator: The Hearing Process”.⁵ This new guideline assigns responsibilities and time frames for each activity in the disqualification process from the notice of opportunity for a hearing through final Agency action. These three procedures combine to address the disqualification process from beginning to end, adding clarity and consistency.

Resources

Based on its assessment of the disqualification process, FDA determined that additional staff and certain organizational changes were critical to the timely resolution of these actions. The Office of Good Clinical Practice added a project manager who is responsible for managing all disqualification matters once the investigator is offered an opportunity for a hearing. Also, the Division of Scientific Investigations in the Center for Drug Evaluation and Research added several staff and realigned its Good Clinical Practice Branches. Under the new organizational structure, some of these additional staff members focus primarily on OAI cases, where disqualification proceedings are initiated. The Office of the Chief Counsel also has seen recent increases in staff. With these overall increases, FDA is able to handle disqualification actions more expeditiously. Finally, under the new Staff Manual Guide, FDA highlighted the fact that an administrative law judge (ALJ) can be designated to serve as the presiding officer at disqualification hearings. Although this was an available option in the past, FDA believes this designation will improve consistency and timeliness of the proceedings.

Tracking of Disqualification Matters

Because there are many FDA components involved in resolving disqualification matters, FDA developed a central tracking system and database to help us monitor these proceedings and ensure all time frames are met.

Outreach and Transparency

Keeping institutional review boards (IRBs), clinical investigators, study monitors, and sponsors informed about FDA's regulatory requirements is critical to protecting human subjects involved in FDA-regulated research. This includes its clinical investigator disqualification process.

⁴ See Compliance Program Guidance Manual (CPGM) 7348.811, Chapter 48 – “Bioresearch Monitoring, Clinical Investigators and Sponsor-Investigators, Guidance for FDA Staff”, at www.fda.gov/ICECI/EnforcementActions/BioresearchMonitoring/ucm133562.htm.

⁵ See www.fda.gov/AboutFDA/ReportsManualsForms/StaffManualGuides/ucm052928.htm; effective June 20, 2008.

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To this end, FDA is drafting guidance to explain the disqualification process, the consequences of disqualification on the clinical investigator, and the impact on any ongoing and completed clinical trials in which the disqualified investigator participated.

Transparency is also a key component of FDA's disqualification process, and FDA strives to be as transparent as possible. On FDA's web site, FDA posts all disqualification information permitted by law, including Commissioner's decisions, so that the basis for FDA's action is clear. In addition, to ensure that IRBs, monitors, and study sponsors are aware of all pending and completed disqualification actions, FDA consolidated into one web site⁶ public information about compliance and enforcement activities. Having all relevant disqualification information accessible in one place will help sponsors avoid non-compliant investigators. FDA believes these outreach efforts will contribute to the protection of human subjects participating in FDA-regulated trials.

Debarment

Recognizing that debarment actions also serve as an important tool for protecting the safety of study subjects involved in clinical trials and the integrity of the drug approval process as a whole, in May, 2008, FDA formed a working group to evaluate the procedures used for debarment actions. The working group quickly concluded that the debarment process would benefit from centralized coordination and formal timelines and procedures aimed at facilitating Agency communication regarding potential debarment actions and ensuring efficiency and timeliness at every step. In March of this year, FDA finalized Staff Manual Guide 7712 – Debarment Proceedings (Debarment SMG), which addresses those issues. FDA believes that consolidating responsibilities for debarment actions and establishing written procedures for such actions will help ensure that they are initiated and processed in a timely, efficient, and consistent manner.⁷

As mentioned in the GAO report, the new Debarment SMG consolidates the responsibility for initiating and pursuing debarment actions in one central location. In the past, the individual Centers were responsible for initiating and pursuing debarment actions that related directly to the Centers' product areas. Now, under the Debarment SMG, the Office of Regulatory Affairs' Office of Enforcement (OE) has the responsibility for initiating all debarment actions for the Agency and issuing orders where no hearing has been requested. To execute those responsibilities, OE has recently received clearance to hire a permanent employee to work on debarment actions. In addition, the Debarment SMG contemplates a dedicated staff within the Office of the Commissioner for ruling on requests for hearings and ensuring that legitimate factual disputes are promptly referred for a hearing.

⁶ See www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/ComplianceEnforcement/default.htm.

⁷ See www.fda.gov/AboutFDA/ReportsManualsForms/StaffManualGuides/ucm127622.htm.

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The Debarment SMG also sets forth procedures and timelines for every step of the debarment process—from the timely internal communication of information regarding convictions or other conduct that may trigger debarment to the conclusion of any debarment proceeding once initiated. Under the Debarment SMG, the Agency will now typically debar individuals and firms within a year from the triggering conviction or conduct. FDA notes, however, that it may be appropriate to delay issuing a proposal for permissive debarment if the candidate for debarment is serving time in prison. This approach would maximize the term of the debarment period which would then begin to run as close to the end of the prison sentence as possible.

Consistent with the Debarment SMG, OE, in consultation with other FDA components, may issue additional standard operating procedures and guidance for debarment actions. As noted in the GAO report, OE has since adopted procedures for making determinations and issuing proposals to debar and certain final debarment orders. It incorporates the timelines found in the Debarment SMG and gives step-by-step instructions for processing proposals and final orders issued by OE. As contemplated by the Debarment SMG, OE also has processes in place to regularly receive communications from the United States Department of Justice and FDA's Office of Criminal Investigations about convictions that could give rise to debarment. In addition, OE has drafted an update for the RPM to detail the notification responsibilities of all relevant FDA employees and the time frames for notification found in the Debarment SMG. The RPM will now also outline the types of convictions and conduct that may subject persons to debarment, to help FDA staff identify these persons and notify OE.

In addition to the procedures reflected in the Debarment SMG and evaluated by GAO, FDA also has begun posting pending debarment actions on its web site in the same location as its list of debarred individuals. Making all information regarding completed and pending debarment proceedings available in one place should assist clinical trial sponsors and others within the drug industry to avoid individuals who may be subject to debarment as a result of a criminal conviction or suspected involvement in a criminal scheme.

Responses to GAO's Recommendations

The Agency is pleased that the GAO's recommendations reflect activities already completed or ongoing. Below, FDA addresses each of the GAO's recommendations.

1) Pursue debarment authority for medical devices that is consistent with the current debarment authority for drugs and biologics and prohibit any debarred individual from involvement with drugs, biologics, and medical devices

FDA's authority to prohibit suspect individuals from being involved in the clinical trial process for drug products helps to protect research subjects and ensure the integrity and reliability of data used to support Agency decision making. Providing FDA with the authority to prohibit individuals and companies convicted of certain crimes, or otherwise involved in criminal activity, from being involved in the medical device industry, would benefit the development and approval process for medical devices in the same manner.

FDA's General Comments to the GAO Draft Report Entitled, Oversight of Clinical Investigators: Action Needed to Improve Timeliness and Enhance Scope of FDA's Debarment and Disqualification Processes for Medical Product Investigators (GAO-09-807)

2) Amend FDA regulations to ensure that those who have engaged in misconduct found sufficiently serious to warrant disqualification for one investigational medical product are not able to continue to serve as clinical investigators for any

FDA agrees that if a clinical investigator is disqualified from participating in clinical trials involving one type of investigational article (e.g., drugs), it is generally appropriate that the investigator be prohibited from participating in investigations of any FDA-regulated product. The Agency intends to pursue revisions of its regulations concerning clinical investigator disqualification to effect this change.

The Agency wishes to note, however, that when FDA disqualifies a clinical investigator, not only are the reviewing IRB and study sponsor notified of this action, but the Agency also posts this information on its web site to ensure that other IRBs and sponsors are fully aware of this determination. FDA also provides such information regarding pending actions on this same web site to ensure that sponsors and IRBs, among others, are alerted to the alleged misconduct.

3) Monitor compliance with recently established time frames for debarment and disqualification proceedings and take appropriate action when those are not met

FDA agrees that monitoring its success in meeting the newly established time frames for clinical investigator disqualification and debarment will be very important as FDA strives to improve its timeliness and efficiency in all aspects of both processes. FDA acknowledges its accountability for completing these administrative actions in a timely and consistent manner, so that human subjects are protected and the integrity and reliability of resulting research data are assured.

As noted in the GAO Report, more recently pursued disqualification proceedings have taken far less time overall than those pursued in the past. Since 2008, the Agency initiated eleven disqualification actions, and of those, only the three initiated in 2009 are still pending. These time frames are consistent with the targeted time frames under the new disqualification procedures.

FDA is also beginning to see similar improvements in the debarment process. Until this year, the Agency had averaged two or three debarment proceedings per year over the past decade. Since March 2009, when the new Debarment SMG went into effect, FDA has initiated debarment proceedings against eleven individuals and completed the debarment process for an additional individual. Of the proceedings that have been initiated, four individuals have been debarred, three have requested a hearing and those cases have been referred to the Office of the Commissioner. Five individuals have been issued Proposal to Debar notifications. With the exception of the first full year that FDA was granted debarment authority, FDA has initiated more debarment proceedings in the last six months than in any other year.

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The GAO pointed out that, the more steps taken by an individual to contest the disqualification or debarment, the longer it takes generally to complete the proceeding. FDA agrees with this assessment. Because of fundamental fairness, FDA must allow individuals to pursue all appropriate avenues available to them to contest their disqualification or debarment, including, on occasion, multiple filings of motions and requests for extensions. Although FDA now has procedures in place with recommended time frames, some disqualification and debarment proceedings will exceed those time frames for that reason. However, for those matters that advance consistent with its procedures, FDA anticipates meeting its targeted time frames.

With the newly implemented procedures and dedicated resources, among other efforts, FDA should continue to see timely and efficient resolution of disqualification and debarment actions.

Appendix VIII: GAO Contact and Staff Acknowledgments

GAO Contact

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

Staff Acknowledgments

In addition to the contact named above, Kim Yamane, Assistant Director; Kristen Joan Anderson; Hernán Bozzolo; Cathleen Hamann; Julian Klazkin; Ba Lin; and Jessica C. Smith made key contributions to this report.

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