

Department of Health and Human Services

**OFFICE OF
INSPECTOR GENERAL**

**CHALLENGES TO FDA'S ABILITY TO
MONITOR AND INSPECT FOREIGN
CLINICAL TRIALS**



Daniel R. Levinson
Inspector General

June 2010
OEI-01-08-00510



E X E C U T I V E S U M M A R Y

OBJECTIVE

1. To determine the extent to which sponsors submitted data from foreign clinical trials to support drug- and biologic-marketing applications approved by the Food and Drug Administration (FDA) in fiscal year (FY) 2008.
2. To determine the extent to which FDA monitors and inspects foreign clinical trials that support marketing applications.

BACKGROUND

The Food, Drug, and Cosmetic Act requires all new investigational drugs and biologics to undergo clinical trials on human subjects to demonstrate the safety and efficacy of these products prior to approval for sale in the United States. Through its review of the clinical trial protocol and sponsors' marketing applications and its inspections of clinical trial sites, FDA ensures the rights, safety, and well-being of subjects who participate in these trials and verifies that the clinical trial data collected are both accurate and reliable.

Sponsors that wish to market drugs or biologics in the United States must submit marketing applications to FDA. Sponsors may submit data from foreign and domestic clinical trials to support marketing applications. Sources have estimated that between 40 percent and 65 percent of clinical trials investigating FDA-regulated products are conducted outside the United States. Sponsors may realize benefits from conducting research abroad, such as lower costs in some countries or the ability to conduct larger trials in less time. Despite benefits to sponsors, critics have raised concerns about the increased prevalence of foreign clinical trials, particularly those conducted in developing countries. The concerns cited by medical ethicists include the ability of local regulatory bodies and institutional review boards to adequately monitor clinical trials to protect the rights and welfare of subjects and to ensure data integrity. Other critics question the extent to which the results from foreign clinical trials conducted in developing countries are generalizable to the U.S. population.

We reviewed all marketing applications for drugs and biologics approved in FY 2008 that contained clinical trial data. We used five sources of data in our review: approved FDA marketing applications and corresponding review documents; FDA inspection documents; structured interviews; database of clinical investigators involved with

Investigational New Drug Application (IND) clinical trials; and FDA policies, procedures, and guidance documents. Using these data sources we calculated the number of foreign trials, sites, subjects, and inspections.

FINDINGS

In FY 2008, sponsors relied heavily on data from foreign clinical trials to support their marketing applications for drugs and biologics. Eighty percent of approved marketing applications for drugs and biologics contained data from foreign clinical trials. Over half of clinical trial subjects and sites were located outside the United States. Western Europe accounted for most foreign clinical trial subjects and sites; however, Central and South America had the highest average number of subjects per site. Based on the increase in foreign clinical investigators conducting clinical trials under INDs over the last 10 years and the observations of FDA reviewers, sponsors' reliance on foreign clinical trials for FDA-regulated drugs and biologics appears likely to grow.

FDA inspected clinical investigators at less than 1 percent of foreign sites. FDA inspected clinical investigators at only 1.2 percent of clinical trial sites for applications approved in FY 2008. FDA inspected 1.9 percent of domestic clinical trial sites and 0.7 percent of foreign clinical trial sites. The agency targeted domestic sites and original applications, although inspection files and interviews with medical reviewers indicated the main reason for inspecting a specific site was a large number of enrolled subjects.

Challenges to conducting foreign inspections and data limitations inhibit FDA's ability to monitor foreign clinical trials. FDA may be unaware of some ongoing, early-phase clinical trials because sponsors are increasingly conducting early-phase clinical trials outside the United States without INDs. Logistical challenges and sponsors' submission of clinical trial data in a nonstandard format also hinder FDA's ability to monitor foreign clinical trials. FDA was also unable to account for all clinical trial information because application files were missing or the sponsors failed to provide site locations and subject enrollment in the clinical study reports.

RECOMMENDATIONS

FDA should take steps to improve its system for overseeing foreign clinical trial data. Toward that end, we recommend that:

FDA should require standardized electronic clinical trial data and create an internal database. Requiring sponsors to submit their clinical trial data in a standardized electronic format would help ensure that reviewers had all necessary information from sponsors to effectively analyze the data, enable FDA to create an internal database to systematically cull clinical trial information, and enable FDA to more effectively select sites for inspection and meet its review timelines.

FDA should monitor trends in foreign clinical trials not conducted under INDs and, if necessary, take steps to encourage sponsors to file INDs. As sponsors submit future marketing applications with the results of foreign clinical trials that were not conducted under INDs, FDA should assess whether enrolled subjects were at additional risk and whether clinical trial data collected were both accurate and reliable. Should FDA determine that clinical trials not conducted under INDs compromised the rights, safety, and well-being of subjects or the integrity of the data submitted by sponsors, it should consider taking steps to encourage sponsors to voluntarily consult with FDA on their clinical trial protocols or submit INDs to the agency. FDA could also explore providing incentives to promote these, if it deems them appropriate.

FDA should continue to explore ways to expand its oversight of foreign clinical trials. To improve its oversight of foreign clinical trials, FDA could take the following additional actions:

Continue to develop inspectional agreements with foreign regulatory bodies. By sharing past inspection details as well as future plans, FDA would be better able to maximize its resources allocated to inspections of foreign clinical trial sites. FDA's recent agreement with the European Medicines Agency is a positive step for the agency to extend its oversight capability outside the United States.

Inspect clinical trials in more countries. FDA could target clinical trials in more countries, such as those in countries that the agency has not previously inspected or where Good Clinical Practice standards have only recently been adopted.

Look to new models of oversight. FDA could explore other oversight models, such as a quality risk management approach, to oversee clinical trials.

AGENCY COMMENTS AND OFFICE OF INSPECTOR GENERAL RESPONSE

FDA agreed with all three of our recommendations. It also stated that it has ongoing efforts or is developing new procedures to address each recommendation.

Where appropriate, we made changes to the report based on FDA's technical comments.



T A B L E O F C O N T E N T S

EXECUTIVE SUMMARY	i
INTRODUCTION	1
FINDINGS	10
In FY 2008, sponsors relied heavily on data from foreign clinical trials to support their marketing applications for drugs and biologics	10
FDA inspected clinical investigators at less than 1 percent of foreign sites	14
Challenges to conducting foreign inspections and data limitations inhibit FDA's ability to monitor foreign clinical trials.	17
RECOMMENDATIONS	20
Agency Comments and Office of Inspector General Response ...	22
APPENDIXES	23
A: Detailed Methodology	23
B: Region Definitions	29
C: Subjects and Sites by Country for Marketing Applications Approved in Fiscal Year 2008.	30
D: Number of Subjects and Number of Inspections per Country for Marketing Applications Approved in Fiscal Year 2008 ...	33
E: Agency Comments	34
ACKNOWLEDGMENTS	43



OBJECTIVE

1. To determine the extent to which sponsors submitted data from foreign clinical trials to support drug- and biologic-marketing applications approved by the Food and Drug Administration (FDA) in fiscal year (FY) 2008.
2. To determine the extent to which FDA monitors and inspects foreign clinical trials that support marketing applications.

BACKGROUND

The Federal Food, Drug, and Cosmetic Act requires all new investigational drugs and biologics to undergo clinical trials on human subjects (hereinafter referred to as “subjects”) to demonstrate the safety and efficacy of these products prior to approval for sale in the United States.¹ Through its review of the clinical trial protocol and sponsors’ marketing applications and its inspections of clinical trial sites, FDA ensures the rights, safety, and well-being of subjects who participate in these trials and verifies that the clinical trial data collected are both accurate and reliable.

Sponsors that wish to market drugs or biologics in the United States must submit marketing applications to FDA.² Sponsors may submit data from foreign and domestic clinical trials to support marketing applications. Sources have estimated that between 40 percent and 65 percent of clinical trials investigating FDA-regulated products are conducted outside the United States.^{3, 4} A recent analysis of the ClinicalTrial.gov Web site found that the 20 largest United States-based pharmaceutical companies were conducting one-third of their clinical trials exclusively at foreign sites.⁵

¹ The Federal Food, Drug, and Cosmetic Act of 1938, P.L. 75-717, 52 Stat. 1040 (1938) (amended 2004); 21 U.S.C. §§ 355(i) and 360(j).

² 21 CFR § 314.50 (drugs) and 21 CFR § 601.2 (biologics).

³ Anand, G.; Wang, S.; Whalen, J., “Scrutiny Grows for Drug Trials Abroad,” *The Wall Street Journal*, December 1, 2008.

⁴ Tufts Center for the Study of Drug Development, *Outlook 2009*, 2009, p. 6.

⁵ Cairns, C.; Califf, R.; Glickman, S.; Harrington, R.; McHutchison, J.; and Peterson, E., “Ethical and Scientific Implications of the Globalization of Clinical Research,” *New England Journal of Medicine*, 2009, 360: 816.

Sponsors may realize benefits from conducting research abroad, such as lower costs in many countries.⁶ Foreign clinical trials may also allow sponsors to conduct larger trials in less time because of access to a larger population.⁷ In addition, sponsors may conduct clinical trials in particular countries because it could be a requirement to file for marketing approval in those countries.⁸

Despite benefits to sponsors, critics have raised concerns about the increased prevalence of foreign clinical trials, particularly those conducted in developing countries. The concerns cited by medical ethicists include the ability of local regulatory bodies and institutional review boards (IRB) to adequately monitor clinical trials to protect the rights and welfare of subjects and to ensure data integrity.^{9, 10} Other critics question the extent to which the results from foreign clinical trials conducted in developing countries are generalizable to the U.S. population.¹¹

Clinical Trials

Sponsors generally conduct clinical trials in multiple trial sites (hereinafter referred to as “multisite trials”). These multisite trials often take place in many countries. Sponsors hire clinical investigators to manage the trial at each site. Typically, a single clinical investigator may enroll anywhere from one to hundreds of subjects, depending on the trial phase.

As a drug or biologic proceeds through development, sponsors conduct clinical trials in three phases. Phase 1 evaluates small groups of healthy volunteers to assess the safety of a product and determine dosage. Phase 2 evaluates the efficacy of the product in patients with the condition to be treated. Phase 3 evaluates the safety and efficacy of a product within a larger population.¹²

⁶ Gregory Lopes, “Drug Makers Look East For Testing,” *The Washington Times*, December 8, 2007.

⁷ Ibid.

⁸ Cairns, C., et al., op. cit., p. 817.

⁹ Buchanan, D.; Sifunda, S.; Naidoo, N.; James, S.; and Reddy, P., “Assuring Adequate Protections in International Health Research: A Principled Justification and Practical Recommendations for the Role of Community Oversight,” *Public Health Ethics*, 2008, 1:3 246–257.

¹⁰ Cairns, C., et al., op. cit., pp. 818–819.

¹¹ Ibid, p. 819.

¹² 21 CFR § 312.21.

FDA bases its approval to market a new drug or biologic largely on a review of the pivotal trial results that sponsors submit with marketing applications.¹³ Pivotal trials are generally Phase 3 trials that support the safety and efficacy of the drug or biologic. FDA requires sponsors to submit all other clinical trial results in their marketing applications, in addition to the pivotal trial results.¹⁴

FDA Oversight of Clinical Trials

Investigational New Drug Application. FDA's oversight of a clinical trial begins when a sponsor submits an Investigational New Drug Application (IND) to the agency. Federal law prohibits unapproved drugs and biologics from interstate commerce. The IND provides an exemption from that law.¹⁵ Because interstate commerce laws do not extend to foreign countries, INDs are not necessary for clinical trials conducted exclusively outside the United States.

INDs provide FDA with information on the clinical trial protocol, the qualifications of trial personnel, and assurances that trials will protect subjects' welfare, among other details. FDA has 30 days to review the IND for safety to ensure that research subjects will not be subjected to unreasonable risk.¹⁶ A sponsor may begin its clinical trial 30 days after FDA receives an IND, provided that the agency does not place the study on clinical hold.¹⁷ Thereafter, FDA may choose to inspect a clinical trial while the trial is ongoing.

FDA regulations permit sponsors to submit marketing applications with data exclusively from foreign clinical trials even if they are not conducted under INDs.¹⁸ Sponsors may also submit the results of earlier foreign clinical trials that were not conducted under INDs in support of current INDs.¹⁹ In both instances, FDA regulations require that sponsors conducted the clinical trials in accordance with Good Clinical Practice, which is defined as "a standard for the design, conduct, performance, monitoring, auditing, recording, analysis, and reporting of clinical trials in a way that provides assurance that the

¹³ The term "pivotal trial" is not defined in statute or regulations.

¹⁴ 21 CFR § 314.50(d)(5).

¹⁵ Federal Food, Drug, and Cosmetic Act, op. cit.; 21 U.S.C. § 355(i) and Public Health Service Act of 1944; 42 U.S.C. 262(a).

¹⁶ 21 CFR § 312.42.

¹⁷ 21 CFR §§ 312.40 and 312.42.

¹⁸ 21 CFR § 312.120 and 21 CFR § 314.106.

¹⁹ 21 CFR § 312.23.

data and reported results are credible and accurate and that the rights, safety, and well-being of trial subjects are protected.²⁰ FDA regulations also require that sponsors submit information retrospectively that is largely similar to what would otherwise be required by an IND.²¹

FDA inspections of clinical trial sites. FDA uses onsite inspections to ensure that clinical investigators, sponsors, and IRBs comply with FDA regulations while developing investigational drugs or biologics. Although FDA has the authority to conduct site inspections, it is not required to do so.

In 1977, FDA established the Bioresearch Monitoring Program to develop cross-center guidelines for inspections of clinical investigators, sponsors, and IRBs.²² The main objectives of this program are to “protect the rights, safety and welfare of subjects involved in FDA-regulated clinical trials and to verify the accuracy and reliability of clinical trial data submitted to FDA in support of research or marketing applications.”²³ The Bioresearch Monitoring Program for drugs is managed by the Division of Scientific Investigations and for biologics by the Division of Inspections and Surveillance. Medical reviewers, who are responsible for approving or disapproving a product, consult with Bioresearch Monitoring reviewers to choose which clinical trial sites to inspect. Bioresearch Monitoring reviewers analyze various factors, such as the clinical trial protocol risk, high subject enrollment at one site, and the clinical investigator’s inspection history to determine which sites to inspect.

FDA may conduct inspections at foreign or domestic sites. Most inspections occur after FDA receives a marketing application and largely verify the accuracy of the clinical trial data submitted with the application. FDA may choose to conduct an inspection while a clinical trial is ongoing.

After the inspection, the medical reviewers and Bioresearch Monitoring reviewers discuss inspection findings. FDA may disqualify data from a

²⁰ 21 CFR § 312.120(a)(i).

²¹ For example, 21 CFR § 312.120 includes requirements that sponsors submit the qualifications of all clinical investigators, a record of an independent review committee oversight, an attestation of the study being conducted according to ethical principles, and a detailed summary of the protocol.

²² 21 U.S.C. §§ 355(i), 360(i).

²³ FDA, *Compliance Program Guidance Manual*, Chapter 48.811: “Bioresearch Monitoring—Clinical Investigators and Sponsor-Investigators” (December 8, 2008).

specific subject, site, or trial based on inspection findings.²⁴ FDA also has the authority to disqualify clinical investigators in cases of deliberate and repeated noncompliance.²⁵

Foreign Oversight of Clinical Trials

International guidelines. The World Medical Association developed the Declaration of Helsinki in 1964 to prescribe ethical standards for clinical research.²⁶ The International Conference on Harmonization developed its *Guideline for Good Clinical Practice* as a unified standard for clinical trials in the European Union, Japan, and the United States. The objective of this guideline is to establish “an international ethical and scientific quality standard for designing, conducting, recording, and reporting trials that involve the participation of subjects. Compliance with this standard provides public assurance that the rights, safety and well-being of trial subjects are protected.”²⁷ The guideline has been credited as a model for some countries’ laws and regulations related to clinical trials.

Foreign regulatory agencies. In addition to observing international standards and guidelines, sponsors conducting clinical trials in foreign countries must comply with the applicable local laws and regulations. Regulatory agencies in each country may monitor clinical trials and conduct inspections, but they are not required to share their findings with FDA.

Marketing Application Review Process

To market drugs in the United States, sponsors must submit marketing applications to FDA’s Center for Drug Evaluation and Research (CDER). To market biologics in the United States, sponsors must submit marketing applications to FDA’s Center for Biologics Evaluation and Research (CBER).²⁸ Before sponsors may begin marketing drugs or biologics, CDER or CBER, as appropriate, must approve the

²⁴ Ibid.

²⁵ 21 CFR § 312.70(a)

²⁶ World Medical Association, *World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects*, June 1964.

²⁷ European Medicines Agency, Harmonized Guideline, Tripartite International Committee on Harmonization Topic E6 (R1): *Guideline for Good Clinical Practice*, June 10, 1996.

²⁸ CDER also regulates biologic therapeutics. Hereinafter, we include biologic therapeutics in our discussion and analyses of drugs.

applications, which consist of information on the products, their manufacturing, clinical trials, and labeling.²⁹

A drug-marketing application for a chemical compound previously unapproved by FDA (i.e., a New Molecular Entity) is called a New Drug Application. A marketing application for a biologic is called a Biologic Licensing Application. (Hereinafter, these two application types will be referred to as “original applications.”) Sponsors may also submit data from clinical trials to support efficacy supplements for approved applications. An efficacy supplement proposes a change to an approved drug’s labeling, such as the indication, dosing, or route of administration.³⁰

Regardless of whether a marketing application contains data from foreign sites, FDA’s review process remains the same. When CDER or CBER receives an application, a medical reviewer first determines whether the sponsor has submitted everything necessary to complete its review. Sponsors identify which clinical trials are the pivotal trials. Clinical study reports that provide results and data analyses from these trials and other pertinent trials must be included in the application. If the application is complete, reviewers conduct a series of scientific analyses on the pivotal trial(s) and other supporting data. These analyses include medical, chemistry, pharmacology, and statistical reviews.

Medical reviewers rely primarily on attestations from sponsors that Good Clinical Practices were followed. These attestations are supported by descriptions of the procedures used to ensure compliance with Good Clinical Practices. FDA reviewers also rely on access to all the data and pertinent case reports forms. Meanwhile, Bioresearch Monitoring reviewers analyze data collected from clinical trial site inspections. These reviewers attempt to verify that informed consent was collected, that protocols were followed, and that the clinical trials were conducted in accordance with standard ethical principles.³¹

If the clinical trial results demonstrate the new drug or biologic to be safe and effective and if FDA reviewers determine that the trial was

²⁹ 21 CFR § 314.50 (drugs) and 21 CFR § 601.2 (biologics).

³⁰ 21 CFR §§ 314.3(b) and 314.60.

³¹ FDA, *CDER, Manual of Policies and Procedures*, MAPP 6010.3, Clinical Review Template, July, 9, 2004, p. 13.

conducted properly and the data are valid, FDA grants approval for the sponsor to market the product in the United States.

The Prescription Drug User Fee Act of 1992 requires FDA to complete its review of drug- and biologic-marketing applications in a timely manner.³² FDA generally has 6 months to review a priority marketing application and 10 months to complete a review of a standard marketing application.

Previous Work

A 2001 Office of Inspector General (OIG) report on the globalization of clinical trials found that the number of clinical investigators conducting research outside the United States under INDs increased from 1990 to 1999. The report also found that research was occurring increasingly in countries with little clinical trial experience. The report raised concerns regarding FDA's ability to ensure the same level of protection to subjects enrolled in foreign trials as domestic trials.³³

A 2007 OIG report highlighted data limitations that inhibit FDA's ability to effectively manage inspections of clinical trials. The report found that FDA had limited authority over foreign trials and often did not know that a foreign trial had been conducted until it was completed and its results were submitted to FDA to support a marketing application.³⁴

METHODOLOGY

Scope

We reviewed clinical trial data from all original applications and efficacy supplements for drugs and biologics approved in FY 2008.

Data Sources and Analyses

We used five sources of data in our review: approved FDA marketing applications and corresponding review documents; FDA inspection documents; clinical investigator information from INDs; structured interviews; and FDA policies, procedures, and guidance documents. (See Appendix A for a detailed methodology.)

³² P.L. 102-571.

³³ OIG, *The Globalization of Clinical Trials* (OEI-01-00-00190), September 2001.

³⁴ OIG, *The Food and Drug Administration's Oversight of Clinical Trials* (OEI-01-06-00160), September 2007.

Approved FDA marketing applications and corresponding review documents.

We requested from CDER and CBER a list of all marketing applications for drugs and biologics approved in FY 2008.

CDER's list consisted of 169 marketing applications for drugs. CDER reported that 114 of these marketing applications contained clinical trial data.

CBER's list consisted of 15 marketing applications for biologics. All of these marketing applications contained clinical trial data.

We reviewed the 129 marketing applications reported to contain clinical trial data and corresponding review documents. We used FDA databases to locate the review documents for each application.

We excluded 8 marketing applications from the original 129 that lacked information on clinical trial locations. This resulted in 121 applications from which we calculated the percentage that contained foreign data.

Our populations included 193 complete clinical trials. We used these clinical trials to calculate the number of subjects, sites, and regions.

FDA inspection documents. We obtained from FDA a list of all inspections it conducted for the marketing applications approved in FY 2008 and their corresponding inspection files. We determined that FDA inspected 147 clinical investigators for the marketing applications in our population.

We used a logistic multivariate regression model to predict the probability of FDA inspecting a clinical investigator at a domestic site as opposed to a foreign site for a specific clinical trial within an application.

Clinical investigator information from INDs. We used the Bioresearch Monitoring Information System to identify and conduct a trend analysis of clinical investigators involved in the conduct of IND studies from 1998 to 2008.

Structured interviews. We interviewed 1 reviewer in each of FDA's 18 review divisions responsible for the marketing applications in our population. The interview questions focused on the processes and challenges, if any, when evaluating data from foreign clinical trials. We also interviewed two senior FDA officials to discuss the processes for determining which sites to inspect and challenges to conducting foreign clinical trial inspections.

I N T R O D U C T I O N

FDA policies, procedures, and guidance documents. We obtained and reviewed all relevant policies, procedures, and guidance documents issued by FDA for accepting marketing applications supported by foreign clinical trials.

Limitations

Our analysis of marketing applications was limited to 1 year of data. Additionally, we did not verify the information provided by FDA, such as the number of applications approved and the number of inspections. Lastly, we were unable to collect information about the number of subjects at the site level, so we could not identify the largest sites for a clinical trial.

Standards

This study was conducted in accordance with the *Quality Standards for Inspections* approved by the Council of the Inspectors General on Integrity and Efficiency.

FINDINGS

In FY 2008, sponsors relied heavily on data from foreign clinical trials to support their marketing applications for drugs and biologics

In FY 2008, FDA approved 129 marketing applications containing clinical trial data: 114 for drugs and 15 for biologics.

Of these, 121 applications contained sufficient information to determine whether sponsors submitted foreign or domestic clinical trial data: 106 for drugs and all 15 for biologics. FDA was unable to locate the other eight marketing applications.

Eighty percent of approved marketing applications for drugs and biologics contained data from foreign clinical trials

Sponsors submitted 91 marketing applications for drugs containing at least 1 foreign clinical trial site (86 percent). Nine of these applications had exclusively foreign data.

Sponsors submitted six marketing applications for biologics containing at least one foreign clinical trial site (40 percent). One of these applications contained exclusively foreign data. (See Table 1 for details.)

Table 1: FDA Marketing Applications for Drugs and Biologics Containing Clinical Data Approved in FY 2008

Marketing Applications	Drugs	Biologics	Drugs and Biologics
Applications With Only Domestic Data	15	9	24
Applications With Foreign and Domestic Data	82	5	87
Applications With Only Foreign Data	9	1	10
Totals	106	15	121

Note: These numbers are based on 121 applications with sufficient information to determine whether the data were foreign or domestic.

Source: OIG analysis of FDA marketing applications approved in FY 2008.

Over half of all clinical trial subjects and sites were located outside the United States

Seventy-eight percent of all subjects who participated in clinical trials were enrolled at foreign sites; 54 percent of all trial sites were foreign. Marketing applications for both drugs and biologics had about half foreign and half domestic trial sites; however, marketing applications for biologics had a much higher percentage of subjects enrolled at foreign sites. (See Table 2 for details.)

FINDINGS

Table 2: Number and Percentage of Foreign Subjects and Sites From Clinical Trials Supporting Drug- and Biologic-Marketing Applications Approved in FY 2008

	Drugs	Biologics	Drugs and Biologics
Number of Foreign and Domestic Subjects	92,859	206,842	299,701
Number of Foreign Subjects	52,820	179,712	232,532
Percentage of Foreign Subjects	56.9%	86.9%	77.6%
Number of Foreign and Domestic Trial Sites	11,227	717	11,944
Number of Foreign Trial Sites	6,129	356	6,485
Percentage of Foreign Trial Sites	54.6%	49.7%	54.3%

Note: These numbers are based on data from 193 clinical trials with complete subject and site information.

Source: OIG analysis of FDA marketing applications approved in FY 2008.

Fifty-seven percent of subjects participating in clinical trials supporting marketing applications for drugs were enrolled at foreign sites. These sites accounted for 55 percent of all trial sites in marketing applications for drugs. The average number of subjects per trial site was similar for foreign and domestic sites: nine at foreign sites and eight at domestic sites.

Eighty-seven percent of subjects who participated in clinical trials supporting marketing applications for biologics were enrolled at foreign sites. These sites accounted for half of all trial sites in marketing applications for biologics. The average number of subjects per site was much greater at foreign sites: 505 at foreign sites versus 75 at domestic sites.

Marketing applications for biologics often contain extremely large clinical trials. For example, 1 trial in Sweden enrolled almost 83,000 subjects at 14 sites, with an average number of subjects per site of almost 6,000. This trial partially explains the large difference in the number and percentage of foreign subjects in applications for biologics compared to drugs.

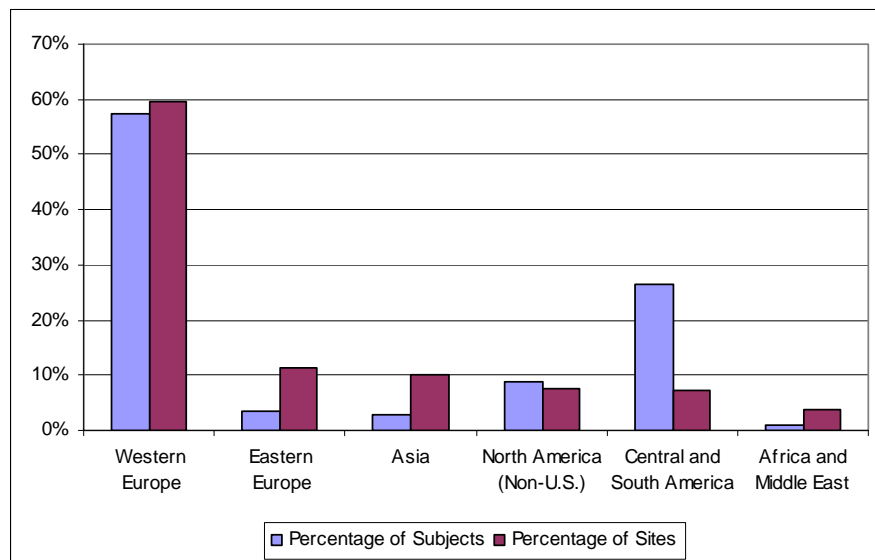
Western Europe accounted for most foreign clinical trial subjects and sites

Sponsors submitted marketing applications with over 200,000 subjects enrolled at over 6,500 foreign sites. Within these applications, Western Europe accounted for 58 percent of subjects enrolled at foreign sites and 60 percent of foreign sites. Although Western Europe accounted for

FINDINGS

most of the subjects enrolled at foreign sites, Central and South America also enrolled a significant number. This region contained 26 percent of all subjects enrolled at foreign trial sites, but it accounted for only 7 percent of foreign sites. (See Graph 1 for details. Also see Appendix B for regional definitions.)

Graph 1: Percentage of Foreign Clinical Trial Subjects and Sites by Region for FDA Marketing Applications Approved in FY 2008



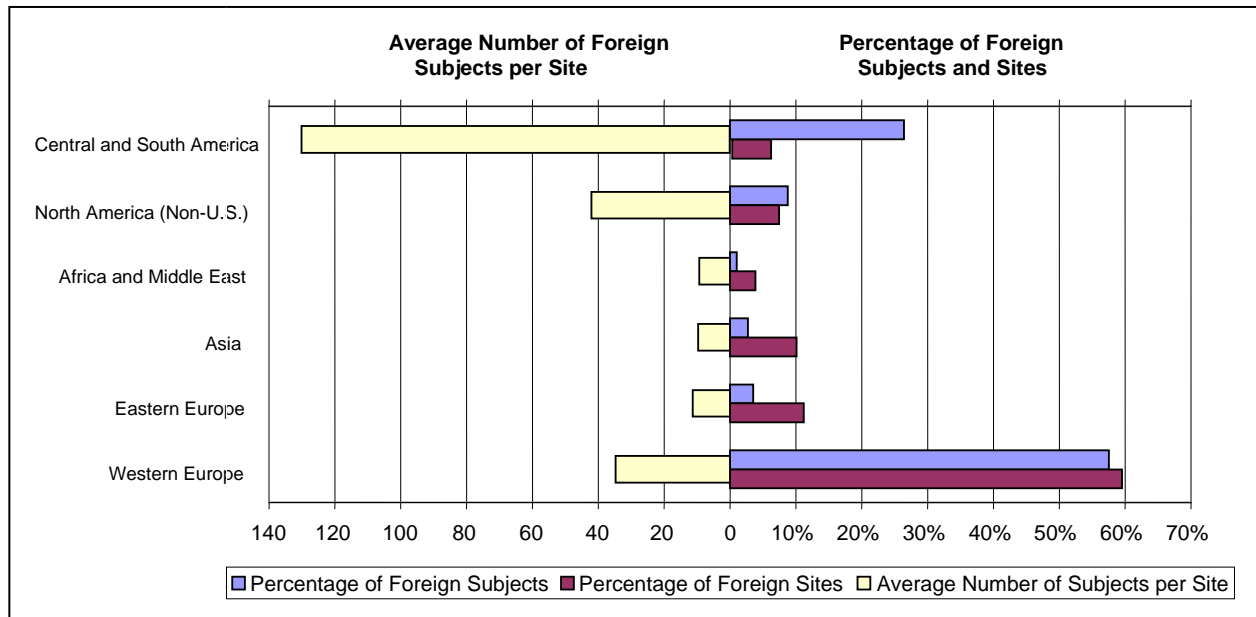
Note: These numbers are based on data from 193 clinical trials with complete subject and site information.

Source: OIG analysis of FDA marketing applications approved in FY 2008.

Central and South America had the highest average number of subjects per site compared to other foreign regions that enrolled clinical trial subjects. The average number of subjects per site was more than three times as large for Central and South American countries as for Western European countries. (See Graph 2 for more details. Also see Appendix C for country-specific data.)

FINDINGS

Graph 2: Average Number of Subjects per Foreign Site Contrasted With Percentage of Foreign Subjects and Sites by Region for FDA Marketing Applications Approved in FY 2008



Note: These numbers are based on data from 193 clinical trials with complete subject and site information.

Source: OIG analysis of FDA marketing applications approved in FY 2008.

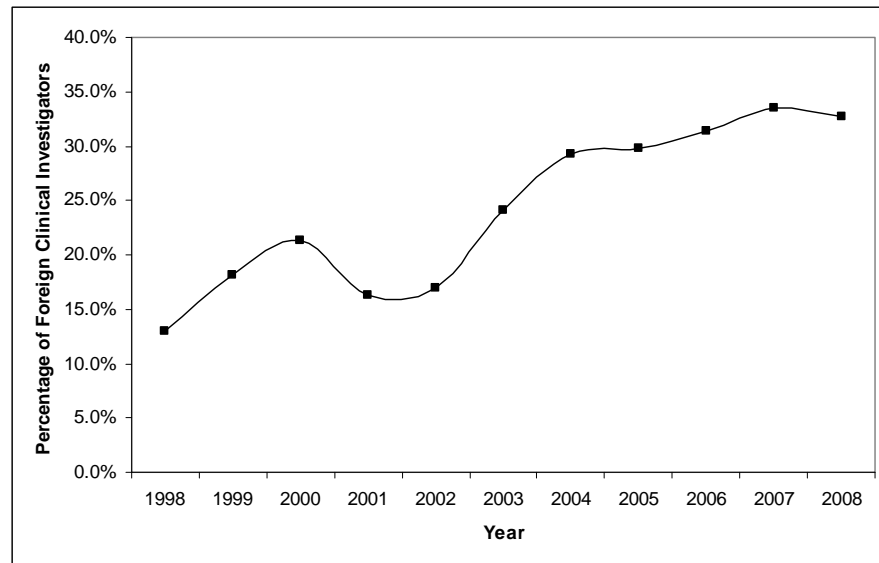
Reliance on foreign clinical trials for FDA-regulated drugs and biologics appears likely to grow

The percentage of foreign clinical investigators conducting clinical trials under INDs has more than doubled over the past decade.³⁵ (See Graph 3 for details.) Clinical trials may take several years to complete before they appear in a marketing application. Therefore, the increase in foreign clinical investigators conducting trials under INDs will not lead to an immediate increase in the use of foreign clinical trial data. Rather, this increase in foreign clinical investigators suggests a possible increase in foreign clinical trial data in future marketing applications.

³⁵ Only CDER tracks the number of foreign clinical investigators who are conducting research under INDs.

FINDINGS

Graph 3: Trend in Foreign Clinical Investigators as a Percentage of All Clinical Investigators Identified in INDs From 1998 to 2008



Source: OIG analysis of FDA's Bioresearch Monitoring Information System data from 1998 through 2008.

FDA reviewers indicated the trend is likely to continue. Twelve of eighteen medical reviewers who commented on trends noted that sponsors' use of foreign data is increasing. Reviewers cited Western and Eastern Europe, Central and South America, and China and India as regions or countries in which sponsors are conducting more clinical trials. FDA reviewers expect more clinical trials from these regions or countries to support marketing applications in the coming years.

FDA inspected clinical investigators at less than 1 percent of foreign sites

Clinical trial site inspections are an important part of FDA's oversight of clinical trials, both

foreign and domestic. The agency uses them to verify the quality and integrity of clinical trial data and to ensure that subjects were protected. However, inspections are not the only oversight mechanism available. FDA also reviews study protocols during the IND phase. In addition, regulatory authorities in other countries sometimes conduct inspections, although the results of these inspections are not necessarily

FINDINGS

shared with FDA. However, according to FDA, the possibility of an inspection helps keep involved parties aware of their responsibilities.³⁶

FDA inspected clinical investigators at few clinical trial sites overall

FDA inspected clinical investigators at 1.2 percent of clinical trial sites for drug- and biologic-marketing applications approved in FY 2008.³⁷ FDA inspected investigators at 0.7 percent of foreign clinical trial sites compared to 1.9 percent of domestic clinical trial sites. (See Table 3 for more details and Appendix D for additional information.)

Table 3: Number and Percentage of Clinical Investigator Inspections at Domestic and Foreign Sites for FDA Marketing Applications Approved in FY 2008

Site Location	Number of Sites	Number of Inspections	Percentage of Sites Inspected
Domestic	5,459	102	1.9%
Foreign	6,485	45	0.7%
Overall Total	11,944	147	1.2%

Note: These numbers are based on data from 193 clinical trials with complete subject and site information.

Source: OIG analysis of FDA marketing applications approved in FY 2008.

FDA inspected clinical investigators at trial sites in 20 of the 72 countries identified in our review. For the clinical trials in our population, of the almost 12,000 clinical trial sites, 16 percent were located in the 52 countries in which FDA conducted no inspections. Of the almost 300,000 subjects, 21 percent were located in these countries. Of note, some of the countries in which FDA conducted no inspections had clinical trials that enrolled a large number of subjects. (See Table 4 for details.) For example, Peru had the fourth largest subject enrollment in our review, yet FDA inspected no trials there for marketing applications in our population.

³⁶ OIG, *The Food and Drug Administration's Oversight of Clinical Trials* (OEI-01-06-00160), September 2007, p. 32.

³⁷ This percentage is similar to that presented in the September 2007 OIG report entitled *The Food and Drug Administration's Oversight of Clinical Trials*. That report estimated that FDA inspected about 1 percent of clinical trial sites from FYs 2000–2005. This estimate was based on all clinical trial sites, not just those used to support approved marketing applications, and included all inspection types.

Table 4: Countries With a Large Number of Subjects Enrolled in Clinical Trials That Were Not Inspected for FDA Marketing Applications Approved in FY 2008

Country	Number of Subjects
Peru	13,628
Colombia	5,480
Chile	4,949
Panama	4,310
Venezuela	4,258
Nicaragua	4,057
Dominican Republic	4,056
Denmark	3,089
Norway	2,513
Poland	2,306
Total	48,646

Note: These numbers are based on data from 193 clinical trials with complete subject and site information.

Source: OIG analysis of FDA marketing applications approved in FY 2008.

FDA inspections targeted clinical investigators at domestic sites and original applications

Our regression analysis indicated that FDA was 16 times more likely to inspect a clinical investigator at a domestic site than a foreign site and that FDA was 9 times more likely to conduct an inspection for an original application than for an efficacy supplement for drugs and biologics. (See Appendix A for details.)

However, inspection files and interviews with medical reviewers indicated the main reason for inspecting a specific clinical investigator was a large number of enrolled subjects at his or her site. Additional reasons for choosing to inspect an investigator included whether the site had a large effect on efficacy results, had data inconsistencies, had statistical outliers, or was part of an original application.

Additional analysis also indicated that FDA inspected clinical investigators at almost three times as many sites with large enrollments than with small enrollments.³⁸ (See Table 5 for details.) This corresponds with reviewers' statements that sites with a large number of subjects are targeted for inspection.

³⁸ "Larger enrollments" is defined as average number of subjects per site greater than or equal to the median, 7.

FINDINGS

Table 5: Inspections Conducted at Clinical Trial Sites With Larger and Smaller Enrollments for FDA Marketing Applications Approved in FY 2008

Application Type	Average Number of Subjects Per Site Less Than Seven			Average Number of Subjects Per Site Greater Than or Equal to Seven		
	Sites Inspected	Total Sites	Percentage Inspected	Sites Inspected	Total Sites	Percentage Inspected
Original Application	19	224	8.5%	39	151	25.8%
Efficacy Supplement	4	534	0.7%	24	644	3.7%
Total	23	758	3.0%	63	795	7.9%

Note: Seven is the median number of subjects per site for all clinical trials in our population.

Note: The number of sites and the number of inspections in Table 5 are different from those in Table 3. The number of sites in Table 3 is based on the 193 clinical trials with complete subject and site information, and the number of inspections is based on clinical investigator inspections for these clinical trials. The number of sites in Table 5 is based on a count of the countries in which trials were conducted to support each application, and the number of inspections is based on whether an inspection occurred in these countries.

Source: OIG analysis of FDA marketing applications approved in FY 2008 and associated clinical inspections.

Challenges to conducting foreign inspections and data limitations inhibit FDA's ability to monitor foreign clinical trials

FDA is unaware of some ongoing, early-phase foreign clinical trials

If a sponsor has not submitted an IND or consulted with FDA in some other way about its foreign clinical trials, FDA has no way of knowing whether and where clinical trials are taking place. Current regulations allow sponsors to submit data from these trials in support of future INDs or marketing applications. Several medical reviewers reported that sponsors are increasingly conducting early-phase clinical trials outside the United States without INDs. Because it takes several years for sponsors to complete all the clinical trials needed to support safety and efficacy, FDA will be unable to determine the extent of this trend until sponsors submit clinical trial results in their marketing applications several years from the start of the trials.

Early-phase trials may pose more risk for subjects because the drugs or biologics have not been tested widely in humans and because they are being tested in an otherwise healthy population, the members of which have nothing to gain therapeutically. If FDA was aware of early-phase

trials through an IND, it could potentially conduct inspections to ensure that all parties comply with applicable regulations and that subjects are protected. However, without an IND, FDA is unaware that these trials are occurring and has no authority to oversee them.³⁹

Logistical challenges complicate foreign inspections

FDA officials reported on a variety of logistical challenges FDA faces when inspecting clinical investigators at foreign sites. According to these officials, inspectors are generally allowed 1 week, including travel time, to conduct these inspections. FDA is unable to easily extend the inspections if significant compliance issues or other problems arise. Officials also reported that obtaining work visas and translators are obstacles to conducting foreign inspections. Lastly, inspections are expensive and may not always be cost effective. One FDA official told us that as sponsors conduct multisite trials at increasingly more sites, fewer subjects are enrolled at any one site. With inspections costing about \$40,000 each and the additional logistical challenges of conducting inspections at foreign sites, it may be more difficult for FDA to justify a foreign inspection.⁴⁰

FDA is taking steps to maximize its resources for inspecting foreign clinical trials. The agency is piloting a computer-based tool (hereinafter referred to as “site selection tool”) to select inspection sites based on risk factors unique to a particular clinical trial. Further, FDA recently announced an initiative with its European counterpart in which both agencies will share information concerning the planning of and results from Good Clinical Practice inspections. Both initiatives could enable FDA to more efficiently target its resources for riskier foreign clinical trials.

Sponsors submitted clinical trial information in a nonstandard format

FDA recommends that sponsors follow Good Clinical Practice guidelines for submitting clinical trial study reports, in addition to requiring that sponsors submit the complete raw data sets of all clinical trials. These guidelines recommend that sponsors submit trial data displayed by

³⁹ FDA may become aware of a foreign clinical trial not conducted under an IND if the sponsor requests a meeting before filing a marketing application. Sponsors sometimes use such a meeting to resolve questions and issues raised during the course of a clinical investigation. See 21 CFR § 312.47.

⁴⁰ A budget official from the Office of Regulatory Affairs provided the budgeted cost for inspections in FY 2008. The inspection cost is about the same for domestic and foreign inspections.

F I N D I N G S

clinical trial sites when the sites have enough subjects to make such an analysis valuable.⁴¹

Despite the Good Clinical Practice guidelines, sponsors generally submitted clinical study reports in portable document formats, which FDA is unable to directly analyze. Within these documents, the data are presented inconsistently, making it difficult to locate clinical trial information, particularly site locations and subject enrollment. As a result, reviewers generally use the raw data submitted by the sponsors to analyze clinical trial results. Although we did not evaluate raw data files, an FDA official told us these files could be as varied and time consuming to analyze as the clinical study reports. In many cases, FDA staff contacted sponsors multiple times to request data in a format they could analyze. The FDA official reported that nonstandard and missing data adversely affect FDA's ability to review marketing applications and meet timelines prescribed by the Prescription Drug User Fee Act of 1992.⁴²

FDA is taking steps to address nonstandard data submissions. The agency is currently piloting a data management system, which would potentially require sponsors to submit standardized clinical trial data. This data management system would enable medical reviewers to review safety and efficacy data more effectively.⁴³

FDA was unable to account for all clinical trial information

FDA was unable to provide detailed clinical trial data for 29 of the 129 applications within our review. FDA was unable to locate any portion of 8 of these 29 applications. All eight applications were paper.

For the other 21 applications, FDA provided incomplete clinical study reports. Four of these applications were paper and the rest were electronic. In some cases, the sponsors failed to provide site locations and subject enrollment in the clinical study reports, and in other cases, appendixes that were supposed to contain the information were missing.

⁴¹ European Medicines Agency, International Committee on Harmonization, Topic 3, Structure and Content of Clinical Study Reports, p. 22, July 1996.

⁴² 21 U.S.C. § 301.

⁴³ OIG interview with an Office of Critical Path Programs official.



R E C O M M E N D A T I O N S

Sponsors relied heavily on data from foreign clinical trials to support their marketing applications for drugs and biologics approved in FY 2008. The percentage of foreign clinical investigators conducting drug research under INDs has more than doubled over the past decade, and FDA reviewers indicated that the number of marketing applications supported by foreign clinical trials will likely continue to increase.

Meanwhile, FDA inspected few clinical investigators at foreign sites. Our review identified shortcomings, such as data limitations and logistical challenges, that also inhibited FDA's ability to monitor foreign clinical trials effectively.

FDA has taken several steps to address these vulnerabilities, such as developing a site selection tool and drafting industry guidance for standardized clinical trial data. Our review shows that FDA should take additional steps to improve its system for overseeing foreign clinical trial data. Toward that end, we recommend that:

FDA should require standardized electronic clinical trial data and create an internal database

Requiring sponsors to submit all necessary clinical trial data in a standardized electronic format would help ensure that reviewers had all information from sponsors to effectively review the data. It would also enable FDA to create an internal database to systematically cull clinical trial information. Standardized clinical trial data would also enable FDA to more effectively select sites for inspection and meet its review timelines. FDA's data management system under development is a positive step to collecting standardized clinical trial data.

An internal database would enable FDA to conduct trend analyses to determine where sponsors were conducting clinical trials as well as identify areas of risk, such as the number of adverse events at any specific site or the numbers of subjects enrolled at clinical trial sites with histories of noncompliance, more quickly.

FDA should monitor trends in foreign clinical trials not conducted under INDs and, if necessary, take steps to encourage sponsors to file INDs

As sponsors submit future marketing applications with the results of foreign clinical trials that were not conducted under INDs, FDA should assess whether enrolled subjects were at additional risk and whether clinical trial data collected were both accurate and reliable.

Conducting a trial under an IND provides an additional layer of oversight. An IND enables FDA to review the protocol before any

R E C O M M E N D A T I O N S

subjects are enrolled in the trial. An IND also gives FDA more opportunity to ensure data integrity through real-time inspections. FDA may require sponsors to change the protocol or may even prevent the trial from starting if it identifies concerns.

Should FDA determine that clinical trials not conducted under INDs compromise the rights, safety, and well-being of subjects or the integrity of the data submitted by sponsors, it should consider taking steps to encourage sponsors to voluntarily consult with FDA on their clinical trial protocols or submit INDs to the agency. FDA could also explore providing incentives to promote these, if it deems them appropriate. Such incentives may require FDA to seek new legislative authority.

FDA should continue to explore ways to expand its oversight of foreign clinical trials

As sponsors increase the number of foreign clinical trials in support of FDA marketing applications, the agency's current method of using inspections to ensure human subject protections and data validity is becoming increasingly strained. To improve its oversight of foreign clinical trials, FDA could take the following additional actions:

Continue to develop inspectional agreements with foreign regulatory bodies.

By sharing past inspection details as well as future plans, FDA would be better able to maximize its resources allocated to inspections of foreign clinical trial sites. FDA's recent agreement with the European Medicines Agency is a positive step for the agency to extend its oversight capability outside the United States.

Inspect clinical trials in more countries. FDA could target clinical trials in more countries, such as those in countries that the agency has not previously inspected or where Good Clinical Practice standards have only recently been adopted.

We recognize that inspecting more foreign sites would require additional resources; however, doing so would communicate to sponsors, clinical investigators, and IRBs the importance of complying with FDA regulations.

Look to new models of oversight. FDA could explore other oversight models, such as a quality risk management approach, to oversee clinical trials. Although not required to, FDA currently inspects clinical trials sites for almost all original applications. A quality risk management approach could focus on identifying and analyzing risk factors unique to each investigational drug or biologic. After assessing the degree of risk,

R E C O M M E N D A T I O N S

FDA would then be able to determine the appropriate level of oversight. FDA's new site selection tool is a positive example of taking steps to utilize quality risk management principles.

AGENCY COMMENTS AND OFFICE OF INSPECTOR GENERAL RESPONSE

FDA agreed with all three of our recommendations. It also stated that it has ongoing efforts or is developing new procedures to address each recommendation.

To address our recommendation that it require standardized clinical trial data and create an internal database, FDA said that it will continue piloting its site selection tool, and, if the pilot is successful, expand its use of the tool within FDA. The agency added that the data captured by the site selection tool represent a partial solution and that it is considering long-term solutions.

FDA agreed with our second recommendation, that trends in clinical trials should be monitored to assess whether differences exist in data integrity and human subject protections between domestic and foreign clinical trial sites. FDA said that it will continue to assess these trends through inspection data. The agency added that it will explore whether tracking the number of applications with clinical trial data not collected under INDs is feasible, and if so, initiate such tracking.

FDA agreed with our third recommendation and highlighted steps it is taking to expand its oversight of foreign clinical trials. The agency stated that if these steps are successful, it plans to leverage its partnership with the European Medicines Agency to work with other regulatory bodies. In addition, FDA highlighted its efforts to expand outreach and training in Good Clinical Practice concepts worldwide.

Where appropriate, we made changes to the report based on FDA's technical comments.

The full text of FDA's comments is provided in Appendix E.

Detailed Methodology

Scope

We reviewed data from all New Molecular Entities, Biologic Licensing Applications, and efficacy supplements (hereinafter referred to collectively as “marketing applications”) approved in fiscal year (FY) 2008. We reviewed all marketing applications approved in FY 2008 from two Food and Drug Administration (FDA) Centers: the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER).

Data Sources and Data Analyses

We used five sources of data in our review: approved FDA marketing applications and corresponding review documents; clinical investigator information from Investigational New Drug Applications (IND); FDA inspection documents; structured interviews; and FDA policies, procedures, and guidance documents.

Approved FDA Marketing Applications and Corresponding Review Documents

We requested from CDER and CBER a list of all marketing applications for drugs and biologics approved in FY 2008, indicating which marketing applications were supported by clinical trial data. We received the list from CDER in March 2009 and from CBER in June 2009.

CDER’s list consisted of 169 marketing applications for drugs. CDER reported that 114 of these marketing applications contained clinical trial data.

CBER’s list consisted of 15 marketing applications for biologics. All of these marketing applications contained clinical trial data.

We reviewed the 129 marketing applications reported to contain clinical trial data and corresponding review documents. We used one of three FDA databases to locate the review documents for each approved marketing application: the CDER Division File System, the Biologic Licensing Application Action Package Files, or the public online database.⁴⁴

For each marketing application in our population, we used the medical review to determine the pivotal clinical trials that supported the drug’s

⁴⁴ Accessed online at <http://www.accessdata.fda.gov/Scripts/cder/DrugsatFDA/> on March 12, 2010.

efficacy and safety. For New Molecular Entities and Biologic Licensing Applications, when the medical reviews did not specify which trials were pivotal, we instead determined which trials supported the entities' efficacy and safety and considered them the pivotal trials. For efficacy supplements, we reviewed all submitted clinical trials. We recorded the pivotal trials in an Access database.

We located the sponsors' marketing applications in one of the following places: Electronic Common Technical Document System, GlobalSummit, or Electronic or Paper Document Rooms. We reviewed the sponsors' marketing application packages for all pivotal clinical trials. Our review of the Clinical Study Reports within the application packages provided information on the number of subjects, sites, and countries in which the trials were conducted for each pivotal trial. We recorded all information in an Access database.

- Approved marketing application calculations: According to FDA, 129 marketing applications contained clinical trial data. We excluded eight marketing applications that lacked information on clinical trial locations. This resulted in 121 marketing applications from which we calculated the percentage that contained foreign data. Twenty-one additional marketing applications included only enough information to determine whether they contained foreign or domestic clinical trials.
- Clinical trial calculations: The 129 approved marketing applications had 252 clinical trials. To avoid double counting, we excluded 32 trials that supported multiple marketing applications, leaving 220 clinical trials. We excluded 27 clinical trials that lacked complete data on trial locations, sites, or subjects. We used the resulting 193 complete clinical trials to calculate the number of sites, subjects, and regions.
- Subject and site calculations: We counted all randomized subjects for each of the pivotal trials in the original 129 marketing applications. We counted each site that randomized subjects for each of the pivotal trials in our population.

FDA Inspection Documents

We obtained from CDER's Division of Scientific Investigations (DSI) and CBER's Division of Inspections and Surveillance (DIS) a list of all inspections conducted for the marketing applications approved in FY 2008 and their corresponding inspection files. Based on the files provided by the Bioresearch Monitoring Programs at DSI and DIS, we

determined the number of inspections conducted for the 129 approved marketing applications. The files also provided insight into FDA’s process for determining which sites to inspect, inspection locations, and the outcomes of these inspections. We received the following:

- **DSI Data:** We received one spreadsheet in April 2009. The spreadsheet contained 152 inspection records for marketing applications for drugs in our review.

For 15 of these inspections, DSI records indicated that multiple clinical trial records were reviewed at 1 site. To account for this, we added 21 records, bringing the total inspection records to 173.

We eliminated all inspections classified as “Withdrawn” or “Canceled.” We also eliminated inspections with clinical trial names that failed to match the clinical trials in our population. We ended up with 134 CDER inspections.

- **DIS Data:** We received one spreadsheet in April 2009. The file contained 27 inspection records for marketing applications for biologics; we did not eliminate any inspections because of their status classifications.

Table A-1 shows the inspection information for our population.

Table A-1: FDA Inspection Types

Inspection Type	Number of Inspections	Percentage of Inspections
Clinical Investigator	147	91.30%
Clinical Research Organization	4	2.48%
Sponsor	10	6.21%
Overall Total	161	100.00%

Source: Office of Inspector General (OIG) analysis of FDA clinical inspections for applications approved in FY 2008.

- **Inspection data at a site level:** DSI and DIS conducted 161 inspections for the marketing applications in our population. We excluded 14 sponsor and contract research organization inspections that were not clinical investigator inspections, leaving 147 clinical investigator inspections.

We used a logistic multivariate regression model to predict the probability of FDA inspecting a clinical investigator at a domestic site as opposed to a foreign site for a specific clinical trial within an

application.⁴⁵ Our regression model employed a dichotomous response variable that indicates whether FDA inspected a clinical investigator at the site. We considered the following explanatory variables when building our model: domestic versus foreign site, application type, review division, review class, presence of an IND, and average number of subjects per site.⁴⁶ (See Table A-2 for more details.)

Table A-2: Regression Variables

Variables	Type of Variable	Values of Variables
Response Variable:		
Inspection Conducted	Dichotomous	0=No, 1=Yes
Explanatory Variables:		
Review Division	Categorical	CDER or CBER
Review Type	Categorical	Orphan, Priority, or Standard
Average Number of Subjects per Site	Continuous	Range=0.4-12,400
IND	Dichotomous	0=No, 1=Yes
Application Type	Dichotomous	1=Original Application, 2=Efficacy Supplement
Foreign or Domestic Country	Dichotomous	0=Foreign, 1=Domestic

Source: OIG analysis of FDA marketing applications approved in FY 2008 and associated clinical inspections.

We tested the significance of each explanatory variable using the Wald Chi-Square statistic at the $\alpha = 0.05$ level. We also used the Pearson Goodness-of-Fit statistic to evaluate the fit of the model as a whole.

The most parsimonious model consisted only of foreign or domestic country and application type as explanatory variables.⁴⁷ (See Table A-3 for the statistics for the significant predictors in our regression model.)

⁴⁵ The denominator of our regression analysis is different from the denominator used to calculate the percentage of clinical trial sites inspected. The number of clinical trial sites for the latter is 12,039, which is the total number of sites for each clinical trial. The regression uses the total number of countries for a specific clinical trial within an application. Further, clinical trials may be duplicated when they are used to support different applications. The denominator of our regression was 1,632.

⁴⁶ Because of data limitations, we were not able to collect the number of subjects enrolled in each site, but were able to calculate the average number of subjects per site for each country.

⁴⁷ The model had a max-rescaled R-square value of 0.34.

Table A-3: Regression Statistics for Significant Predictors

Explanatory Variable	Coefficient Estimate	P-value	Odds Ratio	95%-Confidence Interval
Domestic vs. Foreign Site	2.76	< 0.0001	15.87	9.69–25.99
Original Application vs. Efficacy Supplement	2.15	< 0.0001	8.57	5.19–14.13
Pearson Goodness-of-Fit Test P-value: 0.62*				

* The Pearson Goodness-of-Fit test's large p-value indicates insufficient evidence for rejecting the null hypothesis that the model fits.

Source: OIG analysis of FDA marketing applications approved in FY 2008 and associated clinical inspections.

We found that review division, review type, and IND did not have a significant role in predicting the likelihood of an inspection when modeled with foreign or domestic country, application type, and average number of subjects per site.

We discovered an interaction between foreign or domestic country and average number of subjects per site and tested a model that included the interaction along with application type. However, we were unable to produce estimates for that model with confidence because of small population sizes and ultimately chose to present the simpler model described above. (See Table A-4 for the odds ratios from that model.)

Table A-4: Odds Ratios for Model With Interaction

Explanatory Variable	Odds Ratio	95%-Confidence Interval
Domestic, Avg. Subj. Per Site < 7	40.16	14.56–110.75
Domestic, Avg. Subj. Per Site >= 7	10.96	5.92–20.27
Original Application vs. Efficacy Supplement	9.64	5.71–16.29

Source: OIG analysis of FDA marketing applications approved in FY 2008 and associated clinical inspections.

Clinical Investigator Information From INDs

We used the Bioresearch Monitoring Information System (BMIS) to identify clinical investigators, contract research organizations, and institutional review boards listed on INDs from 1998 to 2008. BMIS identified a total of 878,419 clinical investigators, contract research organizations, and institutional review boards in this time period. We eliminated all contract research organizations and institutional review boards, leaving 382,491 clinical investigators. Using these data, we then calculated the percentage of foreign investigators.

Structured Interviews

We interviewed 1 reviewer in each of FDA's 18 review divisions responsible for marketing applications in our population. Most were team leaders, who oversaw a group of medical reviewers in their division.

The interview questions focused on the processes and challenges, if any, when evaluating data from foreign clinical trials. We developed and used a structured interview guide. After concluding our first two interviews, we solicited comments from the medical reviewers about the interview guide's content and clarity. We incorporated feedback into the final interview guide used for the remaining 16 medical reviewers. We conducted the interviews in May and June of 2009. At least two OIG staff participated in each telephone interview.

To add context to our understanding, we also interviewed two senior FDA officials from DSI and DIS to discuss the processes for and their experiences with conducting foreign clinical trial inspections. Again, we used a structured interview guide. At least two OIG staff participated in each interview.

FDA Policies, Procedures, and Guidance Documents

We obtained and reviewed all relevant policies, procedures, and guidance documents issued by FDA for accepting marketing applications supported by foreign clinical trials.

Data Analysis Software

We used SAS Software for most of our data analyses.

Limitations

Our analysis of marketing applications was limited to 1 year of data. Therefore, we were unable to conduct a trend analysis of foreign data supporting marketing applications; instead we present a trend of clinical investigators named on CDER's INDs.

Additionally, we did not verify the information provided by FDA, such as the number of applications approved and the number of inspections.

Lastly, we were unable to collect information about the number of subjects at the site level, so we created a variable to represent the average number of subjects per site at the country level. This is a limitation of the regression model, because the average number of subjects per site does not identify the largest sites in a country.

Region Definitions

Africa and Middle East

- Cyprus, Egypt, Israel, Lebanon, South Africa, Tunisia, Turkey

Asia

- Australia, China, Hong Kong, India, Indonesia, Japan, Malaysia, New Zealand, Philippines, Republic of Korea, Singapore, Taiwan, and Thailand

Central and South America

- Argentina, Brazil, Chile, Colombia, Costa Rica, Dominican Republic, Ecuador, Guatemala, Honduras, Nicaragua, Panama, Peru, Uruguay, Venezuela

Eastern Europe

- Belarus, Bosnia and Herzegovina, Bulgaria, Croatia, Czech Republic, Estonia, Georgia, Hungary, Latvia, Lithuania, Montenegro, Poland, Romania, Russia, Serbia, Slovakia, Slovenia, and Ukraine

North America (Non-United States)

- Canada and Mexico

Western Europe

- Austria, Belgium, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Italy, Netherlands, Norway, Portugal, Spain, Sweden, Switzerland, and United Kingdom

➤ A P P E N D I X ~ C

Subjects and Sites by Country for Marketing Applications Approved in Fiscal Year 2008

Table C-1: Country Breakdown for Drug-Marketing Applications Approved in Fiscal Year (FY) 2008

Trial Location	Number of Subjects	Percentage of Subjects	Number of Sites	Percentage of Sites	Average Number of Subjects Per Site
Argentina	1,551	1.7%	113	1.0%	14
Australia	1,586	1.7%	228	2.0%	7
Austria	645	0.7%	71	0.6%	9
Belarus	18	0.0%	3	0.0%	6
Belgium	1,571	1.7%	206	1.8%	8
Bosnia and Herzegovina	3	0.0%	1	0.0%	3
Brazil	1,863	2.0%	187	1.7%	10
Bulgaria	507	0.5%	43	0.4%	12
Canada	3,294	3.5%	363	3.2%	9
Chile	454	0.5%	26	0.2%	17
China	424	0.5%	32	0.3%	13
Colombia	177	0.2%	20	0.2%	9
Costa Rica	1,436	1.5%	15	0.1%	96
Croatia	226	0.2%	24	0.2%	9
Cyprus	3	0.0%	1	0.0%	3
Czech Republic	670	0.7%	69	0.6%	10
Denmark	684	0.7%	83	0.7%	8
Ecuador	50	0.1%	4	0.0%	13
Egypt	17	0.0%	2	0.0%	9
Estonia	345	0.4%	27	0.2%	13
Finland	973	1.0%	74	0.7%	13
France	3,960	4.3%	560	5.0%	7
Georgia	1	0.0%	1	0.0%	1
Germany	7,086	7.6%	1,064	9.5%	7
Greece	538	0.6%	68	0.6%	8
Guatemala	138	0.1%	12	0.1%	12
Hong Kong	190	0.2%	18	0.2%	11
Hungary	930	1.0%	79	0.7%	12
Iceland	59	0.1%	8	0.1%	7
India	384	0.4%	49	0.4%	8
Indonesia	20	0.0%	3	0.0%	7
Ireland	209	0.2%	26	0.2%	8
Israel	720	0.8%	81	0.7%	9
Italy	2,910	3.1%	388	3.5%	8
Japan	481	0.5%	75	0.7%	6

continued on next page

A P P E N D I X ~ C

Table C-1: Country Breakdown for Drug-Marketing Applications Approved in FY 2008 (Continued)

Trial Location	Number of Subjects	Percentage of Subjects	Number of Sites	Percentage of Sites	Average Number of Subjects Per Site
Latvia	133	0.1%	11	0.1%	12
Lebanon	42	0.0%	4	0.0%	11
Lithuania	262	0.3%	19	0.2%	14
Malaysia	142	0.2%	23	0.2%	6
Mexico	892	1.0%	94	0.8%	9
Montenegro	8	0.0%	1	0.0%	8
Netherlands	1,248	1.3%	134	1.2%	9
New Zealand	365	0.4%	38	0.3%	10
Norway	682	0.7%	78	0.7%	9
Panama	249	0.3%	10	0.1%	25
Peru	234	0.3%	26	0.2%	9
Philippines	367	0.4%	23	0.2%	16
Poland	1,849	2.0%	194	1.7%	10
Portugal	371	0.4%	58	0.5%	6
Republic of Korea	409	0.4%	32	0.3%	13
Romania	286	0.3%	23	0.2%	12
Russia	1,226	1.3%	141	1.3%	9
Serbia	75	0.1%	7	0.1%	11
Singapore	170	0.2%	22	0.2%	8
Slovakia	348	0.4%	25	0.2%	14
Slovenia	141	0.2%	10	0.1%	14
South Africa	1,140	1.2%	130	1.2%	9
Spain	2,993	3.2%	378	3.4%	8
Sweden	818	0.9%	83	0.7%	10
Switzerland	262	0.3%	50	0.4%	5
Taiwan	721	0.8%	66	0.6%	11
Thailand	314	0.3%	40	0.4%	8
Tunisia	4	0.0%	2	0.0%	2
Turkey	278	0.3%	28	0.2%	10
Ukraine	69	0.1%	12	0.1%	6
United Kingdom	2,564	2.8%	337	3.0%	8
United States	40,039	43.1%	5,098	45.4%	8
Uruguay	27	0.0%	3	0.0%	9
Venezuela	8	0.0%	3	0.0%	3
Foreign Countries	52,820	56.9%	6,129	54.6%	9
United States	40,039	43.1%	5,098	45.4%	8
All Countries	92,859	100.0%	11,227	100.0%	8

Note: These numbers are based on data from 193 clinical trials with complete subject and site information.

Source: Office of Inspector General (OIG) analysis of Food and Drug Administration (FDA) marketing applications approved in FY 2008.

A P P E N D I X ~ C

Table C-2: Country Breakdown for Biologic-Marketing Applications Approved in FY 2008

Trial Location	Number of Subjects	Percentage of Subjects	Number of Sites	Percentage of Sites	Average Number of Subjects Per Site
Argentina	4,686	2.3%	5	0.7%	937
Australia	143	0.1%	2	0.3%	72
Austria	115	0.1%	2	0.3%	58
Belgium	1	0.0%	1	0.1%	1
Brazil	5,747	2.8%	24	3.3%	239
Canada	2,138	1.0%	14	2.0%	153
Chile	4,495	2.2%	3	0.4%	1,498
Colombia	5,303	2.6%	10	1.4%	530
Czech Republic	590	0.3%	21	2.9%	28
Denmark	2,405	1.2%	12	1.7%	200
Dominican Republic	4,056	2.0%	1	0.1%	4,056
Finland	6,776	3.3%	33	4.6%	205
France	146	0.1%	21	2.9%	7
Germany	679	0.3%	35	4.9%	19
Honduras	4,195	2.0%	1	0.1%	4,195
Hong Kong	100	0.0%	1	0.1%	100
Hungary	13	0.0%	1	0.1%	13
Iceland	710	0.3%	1	0.1%	710
Israel	15	0.0%	3	0.4%	5
Italy	102	0.0%	11	1.5%	9
Mexico	14,078	6.8%	13	1.8%	1,083
New Zealand	170	0.1%	5	0.7%	34
Nicaragua	4,057	2.0%	1	0.1%	4,057
Norway	1,831	0.9%	24	3.3%	76
Panama	4,061	2.0%	1	0.1%	4,061
Peru	13,394	6.5%	5	0.7%	2,679
Poland	457	0.2%	14	2.0%	33
Portugal	9	0.0%	2	0.3%	5
Romania	2	0.0%	1	0.1%	2
Russia	93	0.0%	3	0.4%	31
Serbia	11	0.0%	1	0.1%	11
Singapore	181	0.1%	1	0.1%	181
Spain	435	0.2%	19	2.6%	23
Sweden	93,599	45.3%	47	6.6%	1,991
Taiwan	52	0.0%	2	0.3%	26
Thailand	160	0.1%	1	0.1%	160
United Kingdom	457	0.2%	13	1.8%	35
United States	27,130	13.1%	361	50.3%	75
Venezuela	4,250	2.1%	1	0.1%	4,250
Foreign Countries	179,712	86.9%	356	49.7%	505
United States	27,130	13.1%	361	50.3%	75
All Countries	206,842	100.0%	717	100.0%	288

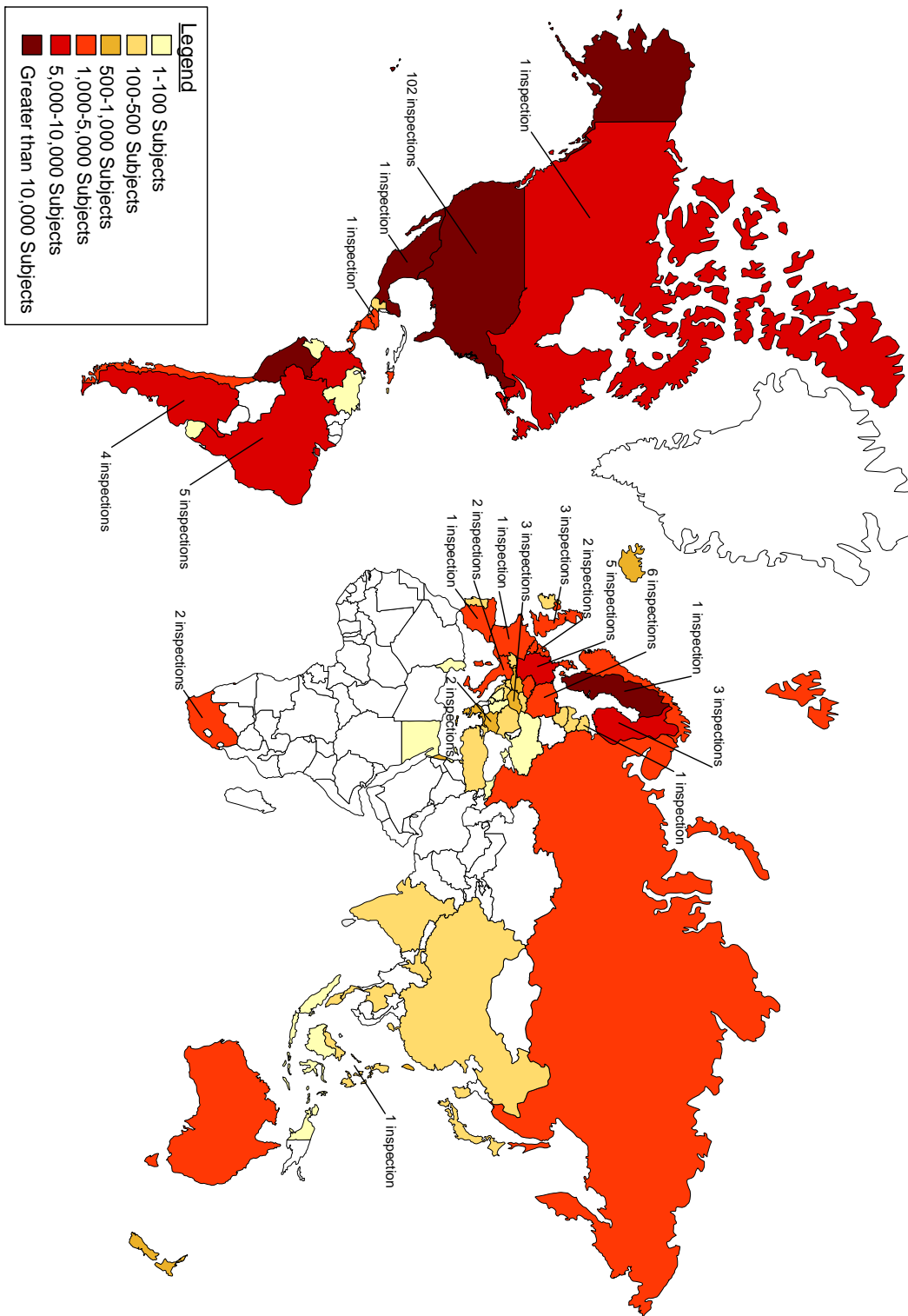
Note: These numbers are based on data from 193 clinical trials with complete subject and site information.

Source: OIG analysis of FDA marketing applications approved in FY 2008.

A P P E N D I X ~ D

Number of Subjects and Number of Inspections per Country for Marketing Applications Approved in Fiscal Year 2008

Figure D-1: Map of Subjects and Inspections per Country



Source: Office of Inspector General analysis of Food and Drug Administration marketing applications approved in fiscal year 2008 and associated clinical trial inspections.

► A P P E N D I X ~ E

Agency Comments



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

DATE: April 23, 2010

TO: Inspector General

FROM: Principal Deputy Commissioner of Food and Drugs

SUBJECT: FDA's Response to OIG's Draft Report Entitled, *Challenges to FDA's Ability to Monitor and Inspect Foreign Clinical Trials*

FDA is providing the attached response to the Office of Inspector General's Draft Report entitled, *Challenges to FDA's Ability to Monitor and Inspect Foreign Clinical Trials (OEI-01-08-00510)*.

FDA appreciates the opportunity to review and comment on this report.

/S/

Joshua M. Sharfstein, M.D.
Principal Deputy Commissioner of Food and Drugs

Attachment

FDA's Response to Office of Inspector General's Draft Report Entitled,
*Challenges to FDA's Ability to Monitor and Inspect
 Foreign Clinical Trials* (OEI-01-08-00510)

The Food and Drug Administration (FDA or Agency) appreciates the opportunity to review and comment on the Office of Inspector General's (OIG's) draft report. In this report the OIG evaluated the extent to which sponsors submitted data from foreign clinical trials to support drug and biologic marketing applications approved by the FDA in fiscal year (FY) 2008 and determined the extent to which FDA monitors and inspects foreign clinical trials that support marketing applications.

The Agency values the OIG's recommendations for improvement and agrees with the main findings in the report. FDA agrees with the recommendations with some clarifications provided in more detail below.

Acceptance of Data Generated Outside the United States

In ensuring the safety and efficacy of medical products and the availability of these products to the public, FDA has long recognized the importance of data generated from clinical trials conducted outside the United States as long as the studies meet regulatory standards and yield results applicable to the United States. Regulations governing the submission of foreign clinical data were first proposed in the early 1980s with final rules published in 1985 for the acceptance of foreign data in New Drug Application [21 CFR 314.106]¹ and in 1987 for acceptance of foreign clinical studies not conducted under an IND [21 CFR 312.120].² With regard to extending its oversight to clinical trials outside the United States, FDA's efforts to ensure data integrity and safety and protection of human subjects must be respectful of the sovereignty of other countries

To address concerns regarding the applicability of data generated from one geographic region to another and to minimize duplicative studies, the guidance document, "Ethnic Factors in the Acceptability of Foreign Clinical Data," was issued in 1998.³ A final rule issued in 2008⁴ permitted the FDA to accept, as support for an investigational new drug application (IND) or an application for marketing approval, a well-designed, well-conducted, non-IND foreign clinical study conducted in accordance with Good Clinical

¹ 21 CFR 314.106 [The acceptance of foreign data in a New Drug Application (NDA)] was proposed in the revisions to the NDA regulations (October 19, 1982), and was finalized on February 22, 1985.

² 21 CFR 312.120 [Foreign clinical studies not conducted under IND]. In the proposed rule revising the IND regulations (June 9, 1983), the preamble states that "the proposal would retain current policy on FDA's acceptance for IND purposes of foreign clinical studies not conducted under an IND. The final rule published on March 19, 1987.

³ International Conference on Harmonization. Ethnic Factors in the Acceptability of Foreign Clinical Data (ICH E-5). CPMP/ICH/289/95. London, United Kingdom: The European Agency for the Evaluation of Medicinal Products; 1998. Available at <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM129507.pdf>

⁴ 21 CFR 312.120

Practices (GCP), including review and approval by an independent ethics committee (IEC), and provided that FDA is able to validate the study data through an onsite inspection, if necessary. The final rule's emphasis on GCP helps to ensure effective human subject protection, provides greater assurance of the quality and integrity of data obtained from these studies, and reflects progress in, as well as the success of, FDA's efforts to harmonize international standards for the conduct of clinical research.⁵ The FDA's guidance on Waiver of Institutional Review Board (IRB) Requirements for Drug and Biological Product Studies provides information for sponsors that wish to conduct a foreign clinical study under an IND when the IEC does not meet all the requirements for IRBs contained in FDA regulations at 21 CFR part 56.⁶ To address questions related to completion of Form FDA 1572 and its applicability to studies involving non-U.S. sites, FDA issued the Draft Guidance, *Frequently Asked Questions - Statement of Investigator* (Form FDA 1572) in July 2008.⁷

Globalization of Clinical Trials

The increasing globalization of clinical trials has presented challenges to both U.S. and international regulatory authorities. FDA has traditionally relied on its own pre-approval compliance inspections to assess data integrity of clinical trial data submitted with applications and to assess whether the rights, welfare, and safety of subjects were protected. However, the growing number of foreign clinical sites and contract research organizations (CROs) challenge FDA's ability to assess foreign clinical trials using the same compliance inspection strategy. For example, the number of active FDA-regulated investigators in foreign countries has increased by 15% each year since 2002.⁸ Resource constraints limit the number of foreign clinical trial site inspections that can be conducted. In addition, inspections are usually conducted after a clinical trial is completed, too late to fix any problems.

At the same time, sponsors have also dramatically expanded the global footprint of their clinical development programs.⁹ Clinical trials may be conducted in emerging regions with a historically limited infrastructure for conducting research. In these emerging regions, the standard of care in medical practice may differ significantly from the United States. As a result, when inter-regional variations in study results have been observed in data submitted

⁵ Final Rule was issued April 2008 and became effective October 2008

⁶ See <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM080613.pdf>

⁷ See <http://edocket.access.gpo.gov/2008/E8-17305.htm>

⁸ Glickman SW, McHuchison JG, Peterson ED, Cairns CB, Harrington RA, Califf RM and Schulman KA. Ethical and scientific implications of the globalization of clinical research. *N Engl J Med.* 2009 Feb 19; 360(8):816-23

⁹ Thiers FA, Sinskey AJ and Berndt ER; Trends in the globalization of clinical trials; *Nature Rev Drug Discov* Jan 2008; 7: 13-14.

to FDA, it has not been easy to ascertain whether these were due to chance, patient selection, ethnic diversity, unblinding, or differences in study conduct.¹⁰ Moreover, disparities in income, education, and access to medical care in these countries also raise concerns about whether study participants' rights are adequately protected.¹¹

To address these challenges, FDA has sought to leverage its resources more efficiently by (1) encouraging sponsors to utilize data standardization in their marketing applications to improve review and analysis of data and facilitate implementation of a site selection model to prioritize sites for inspection; (2) engaging in collaboration and outreach with international regulatory authorities; (3) considering alternative mechanisms of clinical trial oversight both by sponsors and FDA, such as a quality management system approach which emphasizes building quality into the research process. Each of these areas is discussed in more detail in the response to the OIG recommendations, below.

FDA's Oversight of the Conduct of Clinical Trials

OIG's report focuses on the role of FDA's inspections in ensuring data quality and the protection of research participants. The Agency wishes to emphasize that high quality research depends on the active engagement of all stakeholders in clinical trials, including sponsors, CROs, clinical investigators, study staff, IRBs/IECs, and research participants. FDA's regulatory review spans all phases of product development from preclinical to post approval and includes multidisciplinary review of the nonclinical data, the product, the study protocol, statistical analysis plan, clinical data, and inspection results.

FDA's inspections of clinical trials are part of the Agency's broader oversight responsibility. As previously described in our response to the OIG report on FDA's Oversight of Clinical Trials (OEI-02-06-00160), the agency launched its Human Subject Protection (HSP)/Bioresearch Monitoring (BIMO) Initiative to modernize the regulation of clinical trials and bioresearch monitoring.¹² Under this initiative the Agency has reviewed its programs and has focused on improving oversight activities to ensure the protection of human research participants and the integrity and reliability of research data, including oversight of foreign clinical trials.

Comments on Recommendations

For each OIG recommendation, the Agency either has ongoing efforts that will address the recommendation or has initiated development of new procedures that will incorporate the

¹⁰ Temple, R; Use of Non-US Data in NDAs. ASCPT Special Session, Regulatory Considerations of Using Non-US Data in NDAs: Focus on Efficacy, Safety and Clinical Pharmacology. 2009; Access on-line on the ASCPT webpage. <http://www.ascpt.org/annualmeeting2009/presentations/032009/RegulatoryConsiderations.pdf> Ethical and scientific implications of the globalization of clinical research.

¹¹ ICH E5 as above.

¹² See <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2006/ucm108677.htm>

recommendation. FDA offers the following comments on the specific recommendations found in the report. Where necessary, clarifications and caveats are also noted.

(1) FDA should require standardized clinical trial data and create an internal database.

FDA agrees with the OIG recommendation for requiring sponsors to submit standardized electronic clinical data submissions. The lack of standardized data submission, data storage systems, and analysis tools leads to inefficiencies in review and challenges in breadth of oversight of domestic and foreign clinical trials. There are several FDA and Center level efforts underway to develop data standards.

In the short-term, CDER is using existing regulations to support and improve the review of Good Clinical Practice and Human Subject Protection compliance in clinical trials submitted for marketing approval. A CDER pilot program is underway that uses the existing dataset submission framework to request a standardized dataset for analyzing individual clinical sites. An analysis tool for the efficient identification of foreign and domestic clinical investigator sites for inspection as well as a data storage system are being developed to leverage the data for improved analysis capabilities. CDER is currently evaluating methods to expand the tool's ability to detect data irregularities across sites in an application. If successful, the pilot can be expanded to include all marketing applications with clinical data submitted to CDER and would enable more effective targeting of limited inspection resources toward sites with the greatest risk to subject safety and data integrity. The site selection tool is also constructed in such a way to permit expanded use by other FDA Centers.

It should be noted that the pilot program's standard dataset is not a full solution because it only encompasses a small part of the electronic data submitted with an application. Other limitations exist, including the lack of a robust system for uniquely identifying individual clinical investigators. Long-term solutions are being considered.

(2) FDA should monitor trends in foreign clinical trials not conducted under an IND and, if necessary, take steps to encourage sponsors to file an IND.

FDA agrees that trends in clinical trials should be monitored to assess whether any differences exist in data trends and human subject protections between domestic and foreign sites. FDA evaluates results of bioresearch monitoring inspections conducted both domestically and internationally and thus far has not observed distinct differences in non compliance with FDA regulations governing Good Clinical Practices. As research expands in emerging growth regions and more experience accrues in individual countries, the Agency will continue to assess trends in data integrity and human subject protections associated with inspections. In addition, FDA will explore whether tracking the number of applications with clinical data not collected under an IND would be feasible, and if so, will initiate such tracking.

The OIG recommends that the FDA monitor trends in foreign trials not conducted under IND, and should FDA determine that clinical trials not conducted under an IND

compromise the safety of subjects or the integrity of data submitted by sponsors, the OIG recommends that FDA consider taking steps to encourage sponsors to file an IND. Under FDA's existing statutory authority, the Agency cannot require sponsors to file an IND for studies conducted outside the United States. In its oversight activities of clinical trials, the Agency must also be respectful of the sovereignty of individual countries and consider the role of national regulatory authorities. As described in more detail under OIG recommendation 3 (a) below, FDA has been actively engaged in building capacity in areas with a developing research infrastructure and collaborating with the European Medicines Agency (EMA) on information sharing and best practices in Good Clinical Practices (GCP).

FDA is currently assessing the extent to which the ClinicalTrials.gov database mandated under Title VIII of the Food and Drug Administration Amendments Act¹³ could be used to obtain information on foreign clinical trials not conducted under IND, and will explore use of international trial registries in collaboration with regulatory authorities overseeing these registries. For example, the European Medicines Agency is currently developing a public EudraCT¹⁴ portal, the World Health Organization (WHO) maintains its International Clinical Trials Registry Platform,¹⁵ and many other countries are developing their own national registries.

The draft OIG report specifically mentions early phase trials that may pose more risk for subjects and states that if FDA were aware of early phase trials conducted outside the United States through an IND, it could potentially conduct inspections. While the Agency does conduct inspections of earlier phase trials, it does so on a targeted basis, given resource constraints and the need to prioritize inspections to maximize impact. For example, the Center for Biologics Evaluation and Research (CBER) has conducted focused inspection programs to evaluate ongoing studies of cell and gene therapies as well as pediatric clinical studies. Similarly, each year the Center for Devices and Radiological Health (CDRH) conducts targeted inspections of ongoing device studies. The Center for Drug Evaluation and Research (CDER) is initiating routine inspections of earlier phase studies later this year. While the FDA conducts these inspections of earlier phase trials domestically, the Agency is assessing the extent to which international regulatory authorities have controls in place to mitigate risks to subjects in early phase trials, such as the Phase 1 unit accreditation scheme developed by the U.K.'s Medicines and Healthcare products Regulatory Agency (MHRA).¹⁶

¹³ See <http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticAct/FDCAct/SignificantAmendmentstotheFDCAct/FoodandDrugAdministrationAmendmentsActof2007/default.htm>

¹⁴ Available at http://ec.europa.eu/enterprise/sectors/pharmaceuticals/files/pharmacos/docs/doc2003/april/cp-guidance-eudract_230403_en.pdf

¹⁵ Available at <http://apps.who.int/trialsearch/>

¹⁶ See <http://www.mhra.gov.uk/howweregulate/medicines/inspectionandstandards/goodclinicalpractice/index.htm#1>

(3) FDA should continue to explore ways to expand its oversight of foreign clinical trials. *OIG suggests that FDA could take the following additional actions:*

(a) *Continue to develop inspectional agreements with foreign regulatory bodies*

FDA agrees with the OIG's recommendation to further develop inspectional agreements with international regulatory authorities. The globalization of clinical trials has stretched the capacity of regulators to ensure data integrity and the protection of subjects through inspections. Additionally, FDA and other international agencies may duplicate efforts by inspecting the same sponsors and investigators for the same clinical trial whose data are submitted to more than one regulatory agency. This places a burden on sponsors in hosting multiple inspections and in responding to separate inspectional findings.

In September 2009, the FDA and the European Medicines Agency (EMA) launched their GCP Initiative aimed at effective use of inspectional resources through joint inspections; sharing information regarding applications, inspections and good clinical practices in research; and identification of areas of harmonization.¹⁷ If successful, this initiative can save valuable inspectional resources and foster enhanced communications between the FDA and other international regulatory authorities.

Through this program, experience in conducting joint inspections will provide the respective regulatory authorities with an understanding of the health systems, medical practice, and regulatory requirements in foreign countries. Collaboration may also permit the FDA and EMA to exchange best practices for inspections that will improve the consistency, quality, and timeliness of inspections conducted within and across the agencies. This could reduce the time and expense incurred by industry for duplicative inspections and could also help ensure that current review performance commitments are met despite the increase in studies conducted internationally. Experience obtained during the FDA-EMA GCP Initiative could be used as a starting point to expand collaboration with other regulatory authorities.

In addition to collaborations on inspections, FDA is engaged more broadly in outreach and capacity building with other countries around the world. FDA's Office of International Programs has been actively involved in outreach and capacity building since 1997, conducting training and outreach activities throughout the world.

Where FDA has determined that a region is contributing significant volumes of clinical research data to FDA applications, the Agency has endeavored to leverage its own limited inspectional resources by responding through capacity-building training in GCP standards and inspections. The overall goal of the three-phase program is to develop trained trainers in GCP inspections: that is, individuals who can perform and are

¹⁷ See <http://www.fda.gov/InternationalPrograms/FDABeyondOurBordersForeignOffices/EuropeanUnion/EuropeanUnion/EuropeanCommission/ucm189508.htm>

experienced with such functions themselves and who are prepared to train others both within their host authorities and in their regulated community. The program also serves in developing a better mutual understanding of clinical trial oversight as well as relationships that can be sustained beyond completion of the workshops.

In addition, CDER established its International Regulators Forum in 2005 for the exchange of drug regulatory information between CDER and its international counterparts. It is an opportunity for interactive discussion between the attending drug regulatory authorities and CDER staff. Its focus is on the following objectives: to provide in-depth information on CDER's drug review process; to explain CDER's requirements for marketing authorization for new drug applications as well as generics; to elaborate on CDER's GxPs (Good Guidance Practices, Good Review Management Practices, Good Clinical Practices and Good Manufacturing Practices); to discuss pharmacovigilance and CDER's drug safety initiatives; and to equip attendees with knowledge on these topics to enable them to share the information with colleagues in their respective countries. The 10th CDER Forum, to be held April 19-23, 2010, will place a greater emphasis on the review process with an in-depth evaluation of a particular NDA. Specifically, CDER review disciplines will discuss a review that is posted on CDER's Drugs@FDA website.¹⁸

In an effort to respond to the many requests for training from international authorities, CDER has engaged in a series of leveraging activities to help conserve resources while still enabling it to provide training and expertise to other regulatory agencies. One of these leveraging exercises is Pan American Health Organization's (PAHO) Pan American Network for Drug Regulatory Harmonization (PANDRH). Established in 1999, PANDRH provides a framework for involving all of the countries of the Americas and a mechanism for FDA to work with these countries in a coordinated way. Focused on harmonization of drug regulations in the Americas, PANDRH has established a series of working groups and prioritized them as follows: Good Manufacturing Practices, bioequivalence, GCP, and counterfeit drug issues.

In addition to the collaborations and outreach efforts discussed above, FDA recently established international posts in Latin America, Europe, India, China, the Middle East, Africa and Asia. The intent is to leverage the resources of trusted foreign regulatory authorities in these areas and improve the FDA's global presence.

(b) Inspect clinical trials in more countries

The FDA agrees with the OIG's recommendation to inspect clinical trials in countries where the Agency has less inspectional experience or where GCP standards have been recently adopted. The CDER site selection model that is currently being piloted includes as a risk parameter the geographic location of the site so that such countries can be selectively targeted.

¹⁸ See <http://www.accessdata.fda.gov/Scripts/cder/DrugsatFDA/>

(c) Look to new models of oversight

FDA agrees with the OIG's recommendation to consider alternate models of oversight of clinical trials to ensure data quality and the safety of human subjects. Because inspections are usually conducted after studies are completed, problems are often detected too late to correct noncompliance. FDA is currently evaluating ways in which both sponsors and the Agency could adopt a quality systems approach to clinical trial oversight. Such a system would incorporate ongoing monitoring of systems, processes, and data to detect and correct problems in close to real time, while the study is ongoing. Active compliance monitoring would complement traditional auditing activities.

FDA supports a risk-based strategy for quality systems design that focuses on key parameters of risk to trial integrity and data quality as well as subject safety and protection. This strategy recognizes that some aspects of clinical trial conduct represent a higher compliance risk than others, and it permits limited resources to be effectively targeted to those higher-risk activities.

For sponsors, quality systems could cover activities in which errors may undermine the integrity of the study as a whole. These include protocol design, statistical analysis plan development, and Case Report Form design. In addition, quality systems could assess aspects of trial governance such as management of CROs and other third parties, for which recent inspections have identified gaps that contributed to persistent noncompliance and data integrity concerns. Finally, quality systems could consider high-risk trial processes such as randomization and maintenance of blinding, procedures for handling of data, and managing interactions with Data Monitoring Committees and other independent statistical reviewers.

For CDER, a quality systems approach could include augmenting its current site selection model for NDA-related inspections. Additional capabilities could include models that predict how inspectional findings from a few sites translate across an entire application, as well as a learning algorithm that adjusts risk attributes and weights over time as experience with the system provides a greater understanding of risk.



A C K N O W L E D G M E N T S

This report was prepared under the direction of Joyce M. Greenleaf, Regional Inspector General for Evaluation and Inspections in the Boston regional office, and Russell W. Hereford, Deputy Regional Inspector General.

Chris Galvin served as the team leader for this study. Other principal Office of Evaluation and Inspections staff from the Boston regional office who contributed to the report include Carolyn Kenline and Rose Lichtenstein; other central office staff who contributed include Talisha Searcy, Megan Ruhnke, and Heather Barton.

Office of Inspector General

<http://oig.hhs.gov>

The mission of the Office of Inspector General (OIG), as mandated by Public Law 95-452, as amended, is to protect the integrity of the Department of Health and Human Services (HHS) programs, as well as the health and welfare of beneficiaries served by those programs. This statutory mission is carried out through a nationwide network of audits, investigations, and inspections conducted by the following operating components:

Office of Audit Services

The Office of Audit Services (OAS) provides auditing services for HHS, either by conducting audits with its own audit resources or by overseeing audit work done by others. Audits examine the performance of HHS programs and/or its grantees and contractors in carrying out their respective responsibilities and are intended to provide independent assessments of HHS programs and operations. These assessments help reduce waste, abuse, and mismanagement and promote economy and efficiency throughout HHS.

Office of Evaluation and Inspections

The Office of Evaluation and Inspections (OEI) conducts national evaluations to provide HHS, Congress, and the public with timely, useful, and reliable information on significant issues. These evaluations focus on preventing fraud, waste, or abuse and promoting economy, efficiency, and effectiveness of departmental programs. To promote impact, OEI reports also present practical recommendations for improving program operations.

Office of Investigations

The Office of Investigations (OI) conducts criminal, civil, and administrative investigations of fraud and misconduct related to HHS programs, operations, and beneficiaries. With investigators working in all 50 States and the District of Columbia, OI utilizes its resources by actively coordinating with the Department of Justice and other Federal, State, and local law enforcement authorities. The investigative efforts of OI often lead to criminal convictions, administrative sanctions, and/or civil monetary penalties.

Office of Counsel to the Inspector General

The Office of Counsel to the Inspector General (OCIG) provides general legal services to OIG, rendering advice and opinions on HHS programs and operations and providing all legal support for OIG's internal operations. OCIG represents OIG in all civil and administrative fraud and abuse cases involving HHS programs, including False Claims Act, program exclusion, and civil monetary penalty cases. In connection with these cases, OCIG also negotiates and monitors corporate integrity agreements. OCIG renders advisory opinions, issues compliance program guidance, publishes fraud alerts, and provides other guidance to the health care industry concerning the anti-kickback statute and other OIG enforcement authorities.