

Department of Health and Human Services

**OFFICE OF
INSPECTOR GENERAL**

**FDA HAS MADE PROGRESS
ON OVERSIGHT AND
INSPECTIONS OF
MANUFACTURERS OF
GENERIC DRUGS**



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EXECUTIVE SUMMARY: FDA HAS MADE PROGRESS ON OVERSIGHT AND INSPECTIONS OF MANUFACTURERS OF GENERIC DRUGS

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WHY WE DID THIS STUDY

The Office of Inspector General (OIG) received a Congressional request expressing concerns about the safety and quality of generic drugs produced by foreign manufacturers and requesting that OIG evaluate whether the Food and Drug Administration (FDA) is achieving parity in inspections of foreign and domestic manufacturers. In 2012, nearly 80 percent of prescriptions filled in the United States were for generic drugs. But in recent years, several recalls of generic drugs have raised concerns about FDA's oversight of manufacturers.

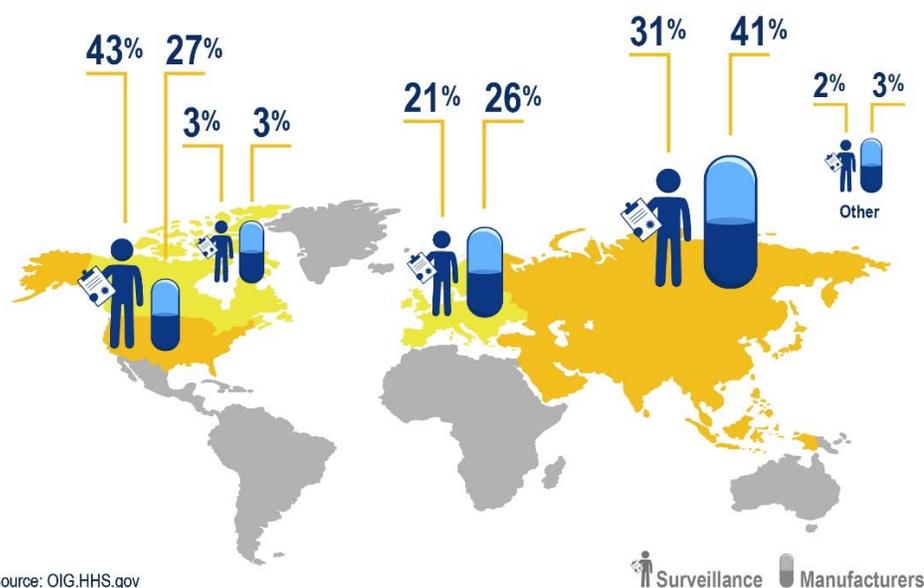
HOW WE DID THIS STUDY

We analyzed FDA data for inspections and registered manufacturers of generic drugs for 2011-2013 to determine the number and types of inspections. We also analyzed FDA data to determine whether manufacturers listed on approved applications had registered with FDA as required. We also analyzed FDA records and interviewed FDA staff to determine the extent to which it is progressing toward achieving parity in domestic and foreign inspections and more efficient processes for inspections.

WHAT WE FOUND

FDA increased its preapproval inspections of manufacturers of generic drugs by 60 percent between 2011 and 2013. However, it did not conduct all of the preapproval inspections requested by its own generic drug application reviewers during this time period. The graphic below illustrates the distribution of generic manufacturers and surveillance inspections worldwide (for more information, see Table 4 in the report).

Distribution of Generic Manufacturers and Surveillance Inspections, Fiscal Year 2013



In 2013, FDA conducted surveillance inspections of all generic manufacturers that it had identified as high risk. FDA also reported progress toward achieving parity in inspections of foreign and domestic manufacturers of generic drugs and ensuring compliance with generic manufacturer registration. Finally, FDA has created some policies and procedures to request manufacturer records in lieu or in advance of an inspection, but has not yet used these procedures to request records.

WHAT WE RECOMMEND

FDA should:

- (1) Conduct outstanding preapproval inspections of manufacturers of generic drugs, where appropriate, which could lead to more timely approval of these drugs.
- (2) Ensure compliance with the requirement for manufacturers of generic drugs to register with FDA as a complete and up-to-date registration database would facilitate the implementation of the agency's plans for conducting inspections.
- (3) Use its authority to request records in lieu or in advance of an inspection. Such requests could increase FDA's capacity for inspections, and review of the records could be completed in advance, which could free up staff time during the onsite portion of the inspection.

FDA concurred with all three recommendations.

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OBJECTIVES

To determine the extent to which:

1. The Food and Drug Administration (FDA) conducts preapproval and surveillance inspections of foreign and domestic manufacturers of generic drugs.
2. FDA made progress toward implementing the Food and Drug Administration Safety and Innovation Act (FDASIA), including achieving parity in inspections of foreign and domestic manufacturers of generic drugs, registering manufacturers of generic drugs, and requesting records in lieu of or in advance of an inspection.

BACKGROUND

Generic drugs are intended to be safe, effective, low-cost alternatives to brand-name drugs. In 2012, nearly 80 percent of prescriptions filled in the United States were for generic drugs.¹ FDA must approve generic drugs before they can be marketed in the United States. FDA's Center for Drug Evaluation and Research (CDER) is responsible for reviewing and approving applications for generic drugs, which are referred to as Abbreviated New Drug Applications (ANDAs). FDA may approve ANDAs without requiring clinical data to prove safety and effectiveness. Instead, applicants must prove that the generic drug is bioequivalent to the brand-name drug—in other words, that it performs in the same manner.²

To be approved, generic drugs must—in most cases—have the same active ingredient, strength, dosage form, labeling, and route of administration as an FDA-approved brand-name drug.³ FDA may reject an application if the manufacturing process is inadequate to ensure the drug's identity, strength, quality, and purity.⁴

¹FDA, *Facts About Generic Drugs*, September 19, 2012. Accessed at <http://www.fda.gov/drugs/resourcesforyou/consumers/buyingusingmedicinesafely/undersandinggenericdrugs/ucm167991.htm> on December 4, 2013.

² FDA, *Abbreviated New Drug Application (ANDA): Generics*. Accessed at <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/default.htm> on August 27, 2014.

³ § 505(j)(2) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. § 355(j)(2)); 21 CFR §§ 314.92 and 314.105(c). Certain deviations from the brand-name drug can be permitted upon FDA grant of a suitability petition. See FD&C Act § 505(j)(2)(C) (21 U.S.C. § 355(j)(2)(C)); 21 CFR §§ 314.93.

⁴ 21 U.S.C. § 355(d)(3).

In recent years, several recalls of generic drugs have raised concerns about FDA's oversight of manufacturers. In May 2013, the generic drug company Ranbaxy pleaded guilty to Federal charges that it failed to follow requirements in the manufacturing process and made false statements to FDA.⁵ Ranbaxy recalled drugs that were produced at two of its facilities in India.

Following the Ranbaxy settlement, the Office of Inspector General (OIG) received a congressional request to evaluate FDA's oversight of manufacturers of generic drugs. The requestor expressed concern about the safety and quality of drugs produced by foreign manufacturers and requested that OIG evaluate whether FDA is progressing toward its goal of achieving parity between inspections of foreign manufacturers and inspections of domestic manufacturers. This evaluation responds to that request.

Inspections of Manufacturers of Generic Drugs

FDA inspects manufacturers of generic drugs to ensure compliance with the FD&C Act and other requirements, including current good manufacturing practices (cGMPs).⁶ Manufacturers include facilities that produce the final dosage form of a drug as well as those that produce active pharmaceutical ingredients in the final product.

Within FDA, CDER and the Office of Regulatory Affairs (ORA) prioritize and conduct inspections. CDER sets manufacturing standards and prioritizes manufacturers for inspection on the basis of risk. ORA plans and conducts the actual inspections.

Preapproval inspections. FDA may inspect the manufacturer(s) prior to approving an ANDA. The applicant must list all manufacturers involved in producing certain components of the drug; however, FDA does not require a preapproval inspection for every manufacturer listed.⁷

CDER established the criteria for determining whether the manufacturers listed on ANDAs need preapproval inspections. If FDA has never inspected the facility before, the agency will conduct a preapproval inspection. In most cases, FDA will also conduct a surveillance inspection

⁵ Department of Justice, Generic Drug Manufacturer Ranbaxy Pleads Guilty and Agrees to Pay \$500 Million to Resolve False Claims Allegations, cGMP Violations and False Statements to the FDA, May 13, 2013. Accessed at <http://www.justice.gov/opa/pr/2013/May/13-civ-542.html> on August 27, 2014.

⁶ FDA cGMP regulations for drugs set out minimum requirements for the methods, facilities, and controls used in the manufacturing, processing, and packaging of a drug.

⁷ Facilities that package generic drugs and conduct bioequivalence testing are also subject to inspection. FDA, *About FDA: What does FDA inspect?* Accessed at <http://www.fda.gov/AboutFDA/Transparency/Basics/ucm194888.htm> on August 27, 2014.

while onsite for a preapproval inspection. ORA schedules inspections on the basis of priority level and available resources. Inspectors seek to verify that the manufacturer provided accurate information in the ANDA and is complying with laws and standards.

Surveillance inspections. FDA also inspects manufacturers to monitor compliance with cGMPs, laws, and regulations. These inspections cover their facilities and procedures for producing drugs.

Once a year, FDA uses a risk-based model to create a list of prioritized manufacturers—both those of generic drugs and those of brand-name drugs—for surveillance inspections.⁸ This list includes production, testing, and packaging facilities both for active pharmaceutical ingredients and finished pharmaceuticals. FDA gives highest priority to manufacturers without prior inspections.

FDA may also conduct a surveillance inspection of a manufacturer on a for-cause basis to investigate a specific problem.

Violations and Enforcement

Inspectors identify violations of FDA regulations on a specific form.⁹ The manufacturer's management may respond in writing with a corrective action plan. FDA makes a final determination of violations after reviewing the form, the written response, the inspector's report, and other evidence collected during the inspection. Either ORA or CDER can make this final determination, depending on the type and results of the inspection.

FDA then classifies the inspection into one of three categories:

- *No Action Indicated.* This classification signifies few or no significant violations of FDA regulations. FDA generally does not require the manufacturer to address any violations.
- *Voluntary Action Indicated.* This classification is used when inspectors find violations that are serious enough to record but do not meet the threshold of regulatory significance.

⁸ FDASIA, P.L. No. 112-144, Title VII § 705.

⁹ FDA, *FDA Form 483 Frequently Asked Questions*. Accessed at <http://www.fda.gov/ICECI/EnforcementActions/ucm256377.htm> on August 27, 2014.

- *Official Action Indicated.* This classification signifies significant violations that may warrant regulatory action. They may lead to an enforcement action if the manufacturer does not correct them.¹⁰

If the result of an FDA inspection is Official Action Indicated, the agency may take action. FDA may issue a warning letter and then follow up with the manufacturer to ensure that it has made the appropriate corrections.¹¹ If the manufacturer does not correct the violations, FDA may request or recommend recalls of marketed products and require new testing of products. FDA may issue an Import Alert to detain and possibly refuse violative drugs. FDA may also pursue other actions, including seizure, injunction, civil penalty, and criminal prosecution.¹² FDA can also bring criminal cases against a manufacturer that is found to be in violation of cGMPs.

Strengthened FDA Oversight of Manufacturers of Generic Drugs

FDASIA increased FDA’s resources for generic drug oversight and strengthened the agency’s authority over manufacturers of generic drugs. Applicable FDASIA provisions include:

Record requests. FDASIA authorized FDA to request records from manufacturers in advance of or in lieu of inspections, such as those related to drug testing, drug manufacturing, facility maintenance, and administration.¹³

Manufacturer self-identification. The Generic Drug User Fee Act (GDUFA) requires manufacturers of generic drugs to identify themselves to FDA.¹⁴ (In this report, we refer to this self-identification process as “registration.”) This requirement includes manufacturers of final-dosage forms and manufacturers of active pharmaceutical ingredients.¹⁵ FDA

¹⁰ FDA, *Field Management Directive—Establishment Inspection Report Conclusions and Decisions (FMD# 86)*. Accessed at <http://www.fda.gov/downloads/ICECI/Inspections/FieldManagementDirectives/UCM382035.pdf> on January 20, 2015.

¹¹ FDA, *About Warning and Close-Out Letters*. Accessed at <http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/ucm278624.htm> on August 27, 2014.

¹² FDA, *Compliance Policy Guides—Fraud, Untrue Statements of Material Facts, Bribery, and Illegal Gratuities*, July 1, 1991, § 120.100.

¹³ FDASIA, Title VII § 706.

¹⁴ Generic Drug User Fee Amendments of 2012 (P.L. No. 112-144, Title III). See also FDA, *Guidance for Industry: Self-Identification of Generic Drug Facilities, Sites, and Organizations*, August, 2012. Accessed at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm316721.htm> on August 27, 2014.

¹⁵ Sites and facilities involved in repackaging and bioequivalence testing of generic drugs must also register with FDA.

created a database that has been available for registration since the start of fiscal year (FY) 2013. FDA maintained no such list of manufacturers of generic drugs prior to FY 2013.

Generic drug user fees. Since FY 2013, FDA has had the authority to collect user fees from manufacturers of generic drugs.¹⁶ These fees are intended to speed ANDA review times and increase FDA's resources for inspecting facilities where generic drugs are manufactured.

Parity in inspections of foreign and domestic manufacturers. FDA committed to achieving parity in surveillance inspections of foreign and domestic drug manufacturers by FY 2017.¹⁷ Section 705 of FDASIA requires a risk-based approach for inspecting drug manufacturers, whether domestic or foreign.

Related Work

In 2010 the Government Accountability Office (GAO) released a report on its review of FDA inspections from FYs 2007 through 2009 of manufacturers of brand-name and generic drugs. GAO found that in FY 2009, FDA inspected 40 percent of domestic drug manufacturers, but only 11 percent of the foreign drug manufacturers in its inventory.¹⁸

METHODOLOGY

Scope

This study focuses on FDA preapproval and surveillance inspections for manufacturers of generic drugs. It assesses the extent to which FDA conducted preapproval inspections and identified violations at manufacturers during calendar years 2011–2013. It also assesses the extent to which FDA conducted surveillance inspections and identified violations at manufacturers in FY 2013.

This study also assesses FDA's progress toward meeting FDASIA goals—specifically, achieving parity in inspections of foreign and domestic manufacturers of generic drugs, creating a registry of those manufacturers, and requesting records in lieu of or in advance of an inspection.

¹⁶ FDASIA, Title III, § 744B.

¹⁷ FDA, *Generic Drug User Fee Act Program Performance Goals and Procedures*. Accessed at <http://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM282505.pdf> on August 27, 2014.

¹⁸ GAO, Drug Safety: FDA Has Conducted More Foreign Inspections and Begun to Improve Its Information on Foreign Establishments, but More Progress Is Needed, GAO-10-961, September 2010.

Data Sources and Analysis

We used seven data sources. A fuller description of these and the ways in which we used them appears in Appendix A.

- FDA's Field Accomplishments and Compliance Tracking System (FACTS), which contains data on all drug manufacturer inspections.
- FDA's User Fee Facility Data Management (UFFDM) database, which contains manufacturer self-reported registration data.
- FDA's Establishment Evaluation System (EES), which FDA uses to manage ANDAs and request preapproval inspections.
- FDA's Compliance Management System (CMS), which contains data on enforcement actions taken by FDA.
- FDA policies and procedures regarding the risk-based model for prioritizing inspections, identifying violations, and taking enforcement action. We also requested policies and procedures for requesting documents in lieu of or in advance of an inspection.
- FDA's lists of generic drug manufacturers prioritized for surveillance inspections for FY 2013.
- Structured interviews with FDA staff in CDER's Office of Generic Drugs and in ORA.

Limitations

FDA did not begin collecting until FY 2013 the data as to which drug manufacturers are involved in producing generic drugs. Therefore, we were unable to determine whether manufacturers that received surveillance inspections prior to FY 2013 produced generic drugs.

We did not analyze the review times for ANDAs, so we were unable to determine whether outstanding preapproval inspections caused delays in ANDA approvals.

Standards

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

FINDINGS

Although FDA increased preapproval inspections of manufacturers of generic drugs from 2011 to 2013, it did not conduct all preapproval inspections requested by its own reviewers of applications for generic drugs

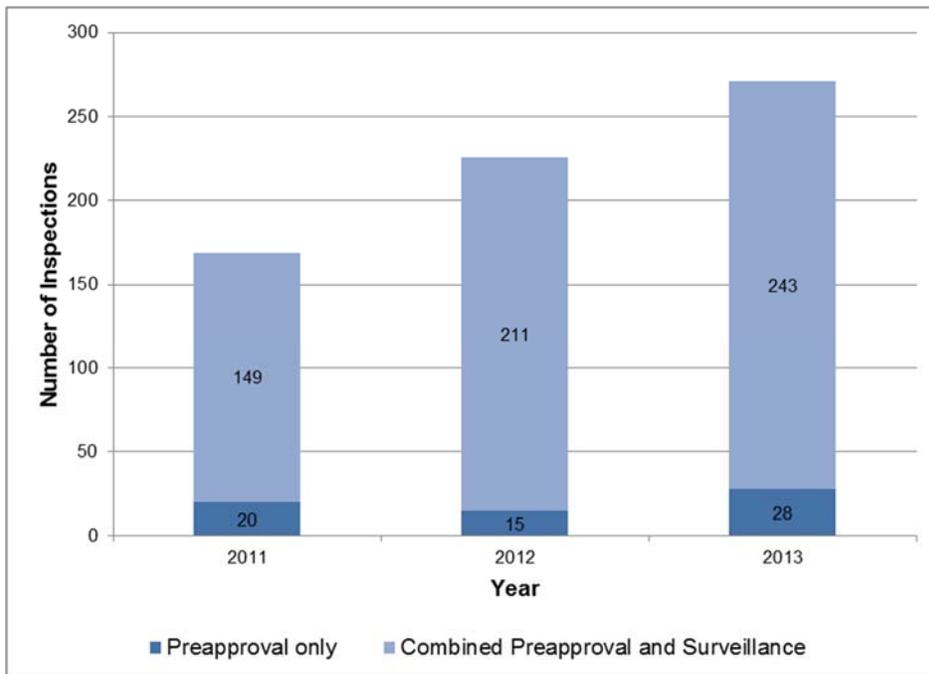
When FDA reviews an ANDA for a generic drug, it evaluates the FDA inspection history of each manufacturer listed on the application. FDA then determines which manufacturers require preapproval inspections and requests that ORA conduct them. In most cases, ORA must conduct requested preapproval inspections before FDA approves an ANDA.

FDA increased its preapproval inspections of manufacturers of generic drugs by 60 percent from 2011 to 2013

FDA increased preapproval inspections every year from 2011 through 2013 (see Figure 1). The GDUFA was implemented in FY 2013, increasing FDA's resources for conducting inspections; the agency collected nearly \$300 million in user fees in FY 2013.¹⁹ FDA used these additional resources for—among other things—hiring and training staff to conduct additional inspections of manufacturers of generic drugs. For this period, FDA conducted the majority of preapproval inspections in conjunction with surveillance inspections.

¹⁹ FDA, *FY 2013 GDUFA Financial Report*. Accessed at <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/UserFeeReports/FinancialReports/GDUFA/UCM395905.pdf> on February 25, 2015.

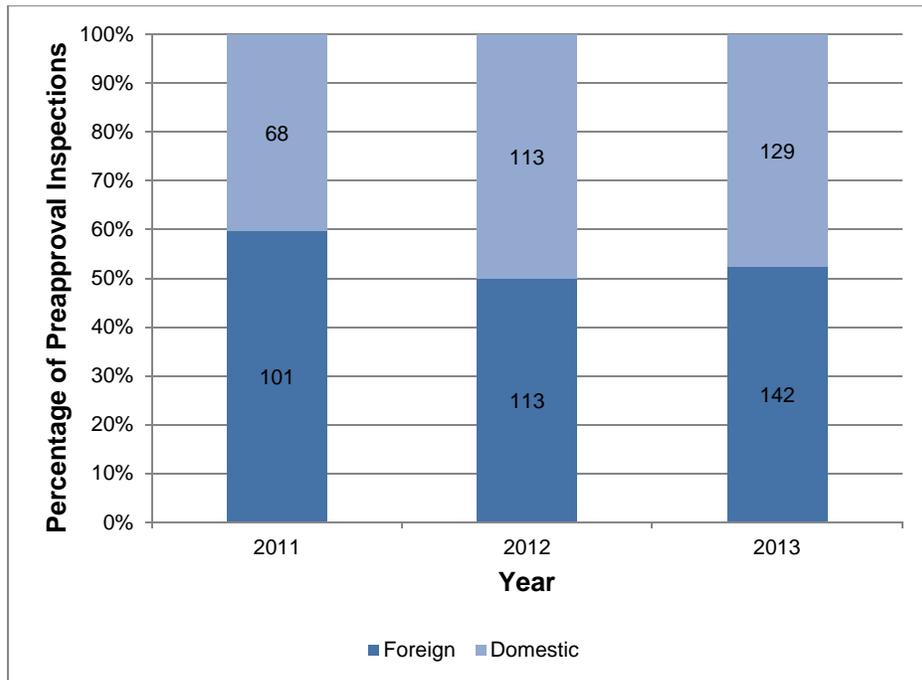
Figure 1: FDA Preapproval Inspections of Manufacturers of Generic Drugs, 2011–2013



Source: OIG analysis of FDA FACTS data, 2011-2013.

Furthermore, FDA conducted more preapproval inspections of foreign manufacturers from 2011 to 2013 than in previous years. FDA performed 101 ANDA preapproval inspections of foreign manufacturers in 2011 and 142 such inspections in 2013. However, the *proportion* of ANDA preapproval inspections conducted at foreign manufacturers as a share of all ANDA preapproval inspections decreased from 60 percent in 2011 to about 50 percent in 2012 and 2013 (see Figure 2).

Figure 2: FDA Preapproval Inspections of Manufacturers of Generic Drugs by Manufacturer Location, 2011–2013



Source: OIG analysis of FDA FACTS data, 2011–2013.

During a preapproval inspection, FDA may find problems that require corrective actions from the manufacturer. The proportion of preapproval inspections with findings of Official Action Indicated remained constant at about 7 percent from 2011 through 2013 (see Table 1). A finding of Official Action Indicated indicates that some type of corrective action would be required before FDA would approve the ANDA. An applicant may decide to work with a new manufacturer if the one listed on the original ANDA receives a classification of Official Action Indicated. About half of preapproval inspections resulted in a final classification of No Action Indicated.

Table 1: Results of FDA Preapproval Inspections of Manufacturers of Generic Drugs, 2011–2013

Final Inspection Classification	Year		
	2011	2012	2013
No Action Indicated, n (%)	74 (52%)	93 (51%)	108 (52%)
<i>Foreign</i>	44	50	52
<i>Domestic</i>	30	43	56
Voluntary Action Indicated, n (%)	59 (41%)	78 (43%)	87 (42%)
<i>Foreign</i>	46	43	48
<i>Domestic</i>	13	35	39
Official Action Indicated, n (%)	10 (7%)	10 (6%)	14 (7%)
<i>Foreign</i>	3	3	7
<i>Domestic</i>	7	7	7
Total	143	181	209

Source: OIG analysis of FDA FACTS data, 2011–2013.

*As of March 31, 2014, 26 inspections conducted in 2011, 45 inspections conducted in 2012, and 62 inspections conducted in 2013 did not have final classifications.

During this period, almost all outstanding preapproval inspection requests were for foreign manufacturers

Although preapproval inspections increased from 2011–2013, as of December 31, 2013, ORA had not conducted all preapproval inspections requested by CDER during that period. Each year, most of those unfulfilled requests were for inspections of foreign manufacturers. For example, 24 percent of preapproval inspections requested in 2011 were outstanding as of December 31, 2013, and all of those requests were for inspections of foreign manufacturers (see Table 2). FDA staff attributed outstanding preapproval inspections to a lack of resources and said that they expect the percentage of inspections conducted to improve with additional funding from user fees from manufacturers of generic drugs.

Table 2: FDA Preapproval Inspection Requests for Manufacturers of Generic Drugs, 2011–2013

Year	Total Preapproval Inspection Requests	All Outstanding Preapproval Inspection Requests* n (% of requests)	Outstanding Preapproval Inspection Requests for Foreign Manufacturers* n (% of outstanding requests)
2011	153	37 (24%)	37 (100%)
2012	267	97 (36%)	94 (97%)
2013	241	155 (64%)	150 (98%)

Source: OIG analysis of FDA FACTS data and FDA List of Requested Preapproval Inspections from 2011–2013.

*As of December 31, 2013.

FDA does not necessarily conduct preapproval inspections in the order in which they are requested. For example, FDA may take drug shortages into account when prioritizing preapproval inspections. Other factors that FDA may consider include staff availability and travel schedules, particularly for foreign inspections.

Outstanding preapproval inspections can delay ANDA approvals.²⁰ However, FDA may have reasons for not conducting all outstanding preapproval inspections. For example, if resources are limited, FDA may review the results of a recent surveillance inspection rather than conducting a separate preapproval inspection. Finally, a preapproval inspection could also be deferred in cases in which an ANDA cannot be approved for many years.

In FY 2013, FDA conducted routine surveillance inspections of all generic manufacturers that it had prioritized as high risk

In the first year of risk-based inspections—FY 2013—FDA prioritized at least 283 manufacturers of generic drugs for routine surveillance inspections and conducted inspections at all of them.²¹ FDA's current risk-based model incorporates the outcomes of previous surveillance inspections, the type of establishment, and the type of product manufactured, among other factors. Of the 283 generic manufacturers that FDA prioritized for inspection in FY 2013, 185 (65 percent) were foreign.

On the basis of these high-priority inspections, FDA required corrective action for 11 generic manufacturers, 2 of which are foreign. FDA took enforcement action against 9 of the 11 manufacturers with classifications of Official Action Indicated.²² These actions included four warning letters—one of which applied to two manufacturers—and four regulatory meetings. The two manufacturers against which FDA did not take enforcement action are both located in the United States.

In FY 2013, FDA conducted additional surveillance inspections beyond those of prioritized manufacturers of generic drugs. In FY 2013, FDA conducted a total of 589 surveillance inspections of generic drug manufacturers, 337 (57 percent) of which were inspections of foreign manufacturers. Most of these inspections were routine surveillance inspections, which are periodic inspections to ensure manufacturers' compliance with cGMPs.

These 589 inspections also included 20 surveillance inspections that FDA performed as followups (i.e., following up on an enforcement action or a

²⁰ OIG's analysis did not address whether outstanding preapproval inspections delayed or prevented the approval of ANDAs.

²¹ In FY 2013, 283 of the 720 unique manufacturers that FDA had prioritized for inspection registered as generic manufacturers. It is possible that some of the remaining 437 manufacturers may have produced generic drugs in FY 2013, but failed to register with FDA as makers of generic drugs.

²² As of March 28, 2014.

previous inspection with a final classification of Official Action Indicated) and 6 inspections performed as a result of consumer complaints.

Table 3: Results of FDA Surveillance Inspections of Manufacturers of Generic Drugs by Location, FY 2013

Final Inspection Classification*	No Action Indicated	Voluntary Action Indicated	Official Action Indicated
Foreign n (%)	116 (42%)	144 (53%)	14 (5%)
Domestic n (%)	83 (41%)	108 (53%)	12 (6%)
Total** n (%)	199 (42%)	252 (53%)	26 (6%)

Source: OIG analysis of FDA FACTS data, FY 2013.

*Data on surveillance-only inspections were available as of FY 2013. As of March 31, 2014, 111 surveillance inspections conducted in 2013 did not have final classifications. One surveillance inspection was referred to the State.

**Percentages in each row do not sum to 100 percent because of rounding.

FDA required corrective action for 26 surveillance inspections conducted in FY 2013 (see Table 3). FDA took action against 20 of the 26 manufacturers with inspection results of Official Action Indicated. Of these 20, 7 are domestic and 13 are foreign. The actions that FDA took included 13 warning letters, 7 import alerts, 4 regulatory meetings, and 1 untitled letter.^{23, 24}

Of the 20 manufacturers against which FDA took action, there were 4 against which it took multiple enforcement actions. All four are located in India:

- *Sentiss Pharma*: FDA issued an import alert and a warning letter.
- *RPG Life Sciences Limited*: FDA issued a warning letter and an import alert that applied to two separate manufacturers owned by this company.
- *Hospira Healthcare India*: FDA issued one import alert and a warning letter.
- *Wockhardt Limited*: FDA issued two warning letters to two different manufacturers owned by this company, as well as two import alerts.²⁵

²³ Section 801 of the FD&C Act explicitly authorizes FDA to refuse admission of articles that appear to violate the Act. FDA's Import Alerts identify the products and firms that meet this criterion.

²⁴ Two warning letters each referenced two inspections that resulted in classifications of Official Action Indicated.

²⁵ One of these warning letters was issued in FY 2014.

In all cases, the warning letters resulted from significant violations of cGMPs for finished pharmaceuticals. The import alerts authorized detaining pharmaceuticals produced at these manufacturers when they were offered for import. For example, Wockhardt Limited's warning letters noted, among other violations, that Wockhardt delayed FDA inspection by denying access to requested documents and obstructing FDA's direct observation of the manufacturing process. FDA also noted problems with laboratory records and stated that it was "particularly concerned about Wockhardt's ability to implement a robust and sustainable quality system," as well as the lack of adequate washing and toileting facilities for workers; FDA had observed urinals without drainage piping and stagnant urine on the facility floor.²⁶

FDA has made progress toward parity and registration of manufacturers of generic drugs, but has not used its authority to request records in lieu of or in advance of an inspection

When FDASIA was signed into law in July 2012, it strengthened FDA's authorities and increased the agency's resources for oversight of manufacturers of generic drugs. When this law was enacted, FDA committed to achieving parity in inspections of foreign and domestic manufacturers of generics by FY 2017. FDA also gained new authorities, including the authority to require manufacturers of generic drugs to register and the authority to request manufacturer records in lieu of or in advance of an inspection.

FDA has made progress toward achieving parity in inspections of foreign and domestic manufacturers

FDA defines "parity" as equal frequency of foreign and domestic inspections plus or minus 20 percent, with both kinds of inspections conducted with "comparable depth and rigor."²⁷ In its FY 2013 GDUFA performance report, FDA reported achieving parity in inspection frequency on the basis of this definition.

Our analysis supported that assertion; of the 589 surveillance inspections that FDA conducted in FY 2013, 337 (57 percent) were of foreign manufacturers. In FY 2013, 1,514 manufacturers of generic drugs registered with FDA, 1,111 (73 percent) of which are foreign. Of these

²⁶ FDA, *Inspections, Compliance, Enforcement, and Criminal Investigations*. Accessed at <http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2013/default.htm> on: October 3, 2014.

²⁷ FDA, *GDUFA Program Performance Goals and Procedures*. Accessed at <http://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM282505.pdf> on September 3, 2014.

foreign manufacturers, 624 are located in Asia and 396 are located in Europe (see Table 4).

Although FDA documented a similar frequency of domestic and foreign inspections in FY 2013, its FY 2013 GDUFA performance report did not fully address the commitment to achieve parity based on risk. To reach that goal, FDA is using a risk-based model to select manufacturers for surveillance inspections without distinguishing between whether the manufacturers are foreign or domestic. FDA planned to report, in FY 2014 and future years, on steps it was taking to schedule and conduct inspections of both domestic and foreign manufacturers according to identical risk factors.

FDA did not report on progress for the second metric of parity, i.e., conducting inspections with comparable depth and rigor. FDA planned to present information addressing this metric in its FY 2014 performance report on GDUFA.²⁸

Table 4: Distribution of Generic Manufacturers and Surveillance Inspections, FY 2013

Country or Region	Number of Manufacturers	Number of Surveillance Inspections
Asia n (%)	624 (41%)	180 (31%)
Europe n (%)	396 (26%)	126 (21%)
Canada n (%)	45 (3%)	20 (3%)
Other n (%)	46 (3%)	11 (2%)
United States n (%)	403 (27%)	252 (43%)
Total* n	1,514	589

Source: OIG analysis of FDA FACTS data and FDA database of manufacturers of generic drugs, FY 2013.

FDA faces a number of challenges in conducting foreign inspections. Because of travel costs, these inspections are more resource intensive. In earlier work on FDA inspections of foreign clinical trials, OIG identified additional logistical challenges that likely also apply to inspections of foreign drug manufacturers—specifically, the time constraints of travel and difficulty in obtaining work visas and translators.²⁹ In recent years, FDA has established international offices in countries such as China and

²⁸ FDA, *FY 2013 Performance Report to the President and Congress for GDUFA*. Accessed at <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/UserFeeReports/PerformanceReports/UCM384177.pdf> on September 3, 2014.

²⁹ OIG, *Challenges to FDA’s Ability to Monitor and Inspect Foreign Clinical Trials*, OEI-01-08-00510, June 2010.

India. These new offices should increase the agency's capacity for foreign inspections by alleviating some of these challenges.

FDA has taken steps to ensure that manufacturers of generics comply with registration requirements, but the registry may be incomplete

The registration of manufacturers of generic drugs began in FY 2013. FDA has encouraged generic manufacturers to register through industry outreach, by releasing draft guidance on registration, and by announcing registration reporting periods in the Federal Register.³⁰ For known generic manufacturers that failed to register in FY 2013, FDA sent letters as reminders to register in the FY 2014 registration period. FDA has issued two warning letters to manufacturers for failing to register in FY 2013. According to FDA, warning letters were sent only to manufacturers that are in the GDUFA Facility Arrears List for failure to pay required annual fees.

As of December 31, 2013, not all known generic drug manufacturers had registered accurately with FDA, despite the agency's efforts. Of the 432 generic drug manufacturers listed on ANDAs approved in 2013, 45 (10 percent) did not match entries in FDA's registry of generic manufacturers as of that date.³¹ Furthermore, 62 percent (28 of 45) of the manufacturers that we were unable to locate in the registry are foreign. Registration provides FDA with information on the universe of generic manufacturers so that it may more effectively conduct surveillance and inspections. FDA staff attributed this discrepancy primarily to generic manufacturers' registering with incorrect identifying information and said that it is working with industry to fix this problem.

FDA made progress toward implementing policies and procedures for requesting manufacturers' records in lieu of or in advance of an inspection, but has yet to use this authority

FDA has started to implement official policies and procedures for requesting records in lieu of an inspection, focusing first on cases involving public health emergencies. In October 2014, FDA published interim policies and procedures for requesting records in the event of a

³⁰ 78 Fed. Reg. 22553 (April 16, 2013).

³¹ As part of its review of our draft report in January 2015, FDA informed us that it had subsequently been able to identify additional manufacturers in the registry. As a result of that further analysis, FDA reports that only eight ANDAs approved in 2013 have no counterpart in the registry and that five of these eight are foreign.

public health incident involving human or animal drugs.³² FDA has not yet used these policies and procedures to request records from a drug manufacturer. However, FDA plans to use these interim policies and procedures to inform the development of policy for use of this authority in inspections broadly, with a focus on foreign surveillance inspections.

Reviewing a manufacturer's documentation of its laboratory and manufacturing practices is a significant component of FDA inspections of drug manufacturers. By conducting this review in advance of visiting a facility, inspectors could focus their onsite time on observing and inspecting areas in need of attention, rather than on reviewing paperwork. For a manufacturer with a positive record in its inspection history, FDA could even go so far as to opt for a record review in lieu of actually visiting the facility.

³² FDA, "Interim Framework for Requesting Records in Advance of or in Lieu of a Drug Inspection in the Event of a Public Health Incident Related to Drugs" (effective October 9, 2014), *FDA Staff Manual Guides*, SMG 9004.1, vol. IV.

CONCLUSION AND RECOMMENDATIONS

Generic drugs are generally less expensive than their brand-name counterparts and therefore are widely used in the United States. In 2012, nearly 80 percent of prescriptions filled in the United States were for generic drugs, and the use of these drugs is increasing.^{33, 34} Ensuring the quality and safety of generic drugs through inspections of manufacturers is essential for maintaining the supply of these drugs. When Congress passed FDASIA in 2012, FDA's resources for such inspections increased significantly.

Our review found that FDA has increased inspections of manufacturers of generic drugs and has made progress toward other inspection-based performance goals resulting from FDASIA. FDA increased the number of preapproval inspections it conducted each year from 2011–2013, and in FY 2013 conducted surveillance inspections of all manufacturers it had prioritized as high-risk. In addition, FDA reported progress toward achieving parity in the frequency of inspections of foreign and domestic manufacturers.

We recommend that FDA:

Conduct outstanding preapproval inspections of manufacturers of generic drugs, where appropriate

As of December 31, 2013, FDA had not conducted all preapproval inspections requested by its own reviewers of applications for generic drugs. Many factors affect the order and timeframe in which FDA conducts such inspections. However, to ensure timely approval of generic drugs, FDA should develop an appropriate timeline to reduce the backlog of preapproval inspections.

Ensure compliance with the requirement for manufacturers of generic drugs to register with FDA

Since FY 2013, all manufacturers producing or planning to produce generic drugs have been required to register with FDA, but our review found that registration data may not be complete. Registration provides FDA with information on the universe of manufacturers producing or

³³FDA, *Facts About Generic Drugs*, September 19, 2012. Accessed at <http://www.fda.gov/drugs/resourcesforyou/consumers/buyingusingmedicinesafely/undersandinggenericdrugs/ucm167991.htm> on December 4, 2013.

³⁴ Health Care Cost Institute. *2012 Health Care Cost and Utilization Report*, September 2013. Accessed at <http://www.healthcostinstitute.org/files/2012report.pdf> on December 9, 2013.

intending to produce generic drugs. To ensure the completeness of this registration information, FDA should continue to:

- cross-check manufacturers listed on approved ANDAs to ensure that all of the manufacturers listed have registered,
- cross-check its list of registered manufacturers against other lists of known generic manufacturers, and
- send warning letters to manufacturers that do not comply with registration requirements.

Such actions enhance FDA's ability to track and oversee manufacturers of generic drugs.

Use its authority to request records in lieu of or in advance of an inspection

In 2012, FDASIA granted FDA the authority to request records in lieu of or in advance of an inspection. This authority could increase FDA's capacity for inspections; record reviews could be completed in advance, rather than using up the inspection staff's time during an onsite inspection. FDA has published interim policies and procedures for using this authority in the event of a public health incident, but the agency is still in the process of determining the most appropriate way to use this authority for surveillance inspections. FDA should establish a plan to use this authority for surveillance inspections and then move expeditiously to implement the plan.

Once FDA implements policies and procedures, FDA could direct its ORA staff to take full advantage of them as a potential way of reducing costs and enhancing flexibility in conducting inspections.

AGENCY COMMENTS AND OFFICE OF INSPECTOR GENERAL RESPONSE

FDA concurred with all three of our recommendations.

In response to our first recommendation, FDA stated that it is working diligently to conduct all outstanding preapproval inspections. FDA continues to expand and train its workforce in support of this goal.

In response to our second recommendation, FDA stated that it will continue to send letters to generic drug manufacturers that fail to register and follow up with warning letters to those that fail to register and pay required annual fees.

In response to our third recommendation, FDA agreed to the use of its new authority to request records in lieu or in advance of an inspection. FDA is developing policies, guidance, and pilot projects to implement this authority.

OIG supports FDA's efforts to improve oversight and inspections of manufacturers of generic drugs. We will continue to monitor these efforts.

For the full text of FDA's comments, see Appendix B.

APPENDIX A

Detailed Data Sources and Analysis

We used seven data sources in our review:

FDA's Field Accomplishments and Compliance Tracking System (FACTS). FACTS includes data on all drug manufacturer inspections. For preapproval inspections, FACTS contains data on whether the inspected manufacturer produced generic drugs. We analyzed FACTS inspection data to determine the number of preapproval inspections conducted from 2011 through 2013. We also analyzed FACTS data to determine the final classifications of these inspections. For surveillance inspections, FACTS does not differentiate between manufacturers of generic drugs and manufacturers of brand-name drugs. As a result, we were able to identify surveillance inspections and their results only for generic manufacturers registered with FDA in FY 2013.

FDA's User Fee Facility Data Management (UFFDM) database. UFFDM contains the data that manufacturers of generic drugs have self-reported to FDA. Because FDA began collecting these data at the start of FY 2013, UFFDM does not contain complete data on generic drug manufacturers that were in operation in 2011 and 2012. We analyzed FY 2013 data along with data from FACTS to determine how many generic drug manufacturers in operation at this time had surveillance inspections in FY 2013.

FDA's Establishment Evaluation System (EES). FDA uses EES to manage ANDAs and request preapproval inspections. We requested EES data on all ANDAs approved from 2011 through 2013. We analyzed these data along with data from UFFDM to determine the number of manufacturers associated with approved ANDAs during that time period as well as the percentage of these manufacturers that registered with FDA as required.

FDA's Compliance Management System (CMS). The CMS database includes data on enforcement actions taken by FDA. We reviewed information on all enforcement actions recommended and taken against manufacturers of generic drugs from 2011 through March 28, 2014, the date FDA extracted data from this system. For manufacturers that CMS indicated had received warning letters in this period, we reviewed the warning letters on FDA's public Web site.

FDA policies and procedures. We reviewed policies and procedures, including those regarding FDA's risk-based model for prioritizing inspections of manufacturers of generic drugs, identifying violations, and

taking enforcement action. Additionally, we requested FDA's policies and procedures for requesting documents in advance or in lieu of an inspection.

FDA's lists of generic drug manufacturers prioritized for surveillance inspections. We requested the list of generic drug manufacturers that FDA prioritized for inspections in FY 2013 using its risk-based model. We compared this list with FACTS data to determine the extent to which FDA completed prioritized inspections.

Structured interviews with FDA staff. We conducted structured interviews with FDA staff in CDER's Office of Generic Drugs and in ORA to obtain a first-person account of how staff prioritize and conduct inspections, decide to take enforcement action, and ultimately approve ANDAs.

APPENDIX B

Agency Comments



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

DATE: March 11, 2014
TO: Inspector General
FROM: Associate Commissioner for Public Health Strategy and Analysis
SUBJECT: FDA's Comments to OIG Draft Report entitled, *FDA Has Made Progress on Oversight and Inspections of Generic Drug Manufacturers*

FDA is providing the attached comments to the Office of Inspection General Draft Report entitled, FDA Has Made Progress on Oversight and Inspections of Generic Drug Manufacturers.

We appreciate the opportunity to review and comment on this draft report before it is published.

/s/

Peter Lurie, MD, MPH

Attachment

APPENDIX B (CONTINUED)

Food and Drug Administration's General Comments to Office of Inspector General's Draft Report

"FDA Has Made Progress on Oversight and Inspections of Generic Drug Manufacturers, OEI-01-13-00600"

The Food and Drug Administration (FDA) welcomes the Office of Inspector General's (OIG) report as a means for assessing FDA's progress towards implementing the Food and Drug Administration Safety and Innovation Act (FDASIA) of 2012, which, among other critical new tools, strengthened our authority over generic drug manufacturers. As part of FDA's responsibility to protect Americans in today's complex global supply environment, this legislation provides FDA with enforcement tools that facilitate and expand its inspection authority to include implementing administrative detention authority that will protect the integrity of the drug supply chain¹, obtaining records during an on-site inspections, directing drug establishment firms to register in the unique facility identifier (UFI) system², and deeming a drug misbranded if an establishment delays, denies, limits, or refuses a drug inspection³.

Working together with our stakeholders, FDA will continue its strategic implementation of both FDASIA and the Generic Drug User Fee Act (GDUFA) by prioritizing these efforts based on the greatest benefit to public health.

Response to OIG Recommendations

Recommendation 1: FDA should conduct outstanding generic preapproval inspections, where appropriate.

FDA concurs with this recommendation. FDA is committed to conducting both generic preapproval and routine inspections in a timely manner. FDA uses a risk-based approach in selecting facilities for pre-approval inspections and continues to refine that approach. FDA is working diligently to conduct all outstanding Pre-Approval Inspections (PAI). As noted in the report, the number of PAIs of generic facilities has steadily risen since the passage of the Generic Drug User Fee Act (GDUFA) and will continue to do so as FDA continues to hire and train its workforce in support of GDUFA programs.

Recommendation 2: FDA should ensure compliance with the requirement for generic drug manufacturers to register with FDA.

FDA concurs with this recommendation.

¹ June 2014 Final Rule "Administrative Detention of Drug Intended for Human or Animal Use <https://www.federalregister.gov/articles/2014/05/29/2014-12458/administrative-detention-of-drugs-intended-for-human-or-animal-use>

² November 2014 Guidance for Industry "Specification of the Unique Facility Identifier (UFI) System for Drug Establishment Registration <http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm421827.pdf>

³ October 2014 Final Guidance for Industry "Circumstances that Constitute Delaying, Denying, Limiting, or Refusing a Drug Inspection" <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM360484.pdf>

APPENDIX B (CONTINUED)

With respect to the recommendation, FDA sends letters to firms that fail to self-identify, and then follows up with warning letters to firms that fail to self-identify and pay required annual fees. FDA believes that continuing these practices will help to ensure compliance with GDUFA self-identification and payment requirements.

Recommendation #3: FDA should also use its authority to request records in lieu or in advance of an inspection.

FDA concurs with this recommendation. FDA agrees that generic firms should self-identify and register their facilities, as required. FDA also agrees to the use of its new authority to request records in lieu of or in advance of an inspection. FDA is actively participating in the development of policies, guidance, and pilot projects to implement this authority. As noted in the report, FDA has prioritized implementing procedures for use in the event of a public health incident, and will continue for planning further use.

As OIG states, use of FDASIA Section 706⁴ in advance of an inspection could lead to efficiencies by allowing inspectors to target time spent on site and potentially increases FDA's capacity for inspections. FDA is supportive of these potential benefits and is seeking to carefully implement the authority by evaluating whether the efficiencies we hypothesize will be gained.

FDA is developing a plan to pilot the use of the authority in a small number of already planned inspections, and the Agency will use the results of that effort to inform its strategy on a broader implementation of the authority.

⁴ Section 706 of FDASIA amends section 704(a) of the FD&C Act by adding subsection (4), which requires "a person that owns or operates an establishment that is engaged in the manufacture, preparation, propagation, compounding, or processing of a drug" to provide FDA, upon request, in advance of or in lieu of an inspection, records or other information that FDA may inspect under section 704(a).

ACKNOWLEDGMENTS

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

Jessica Fagnoli served as the team leader for this study, and Elizabeth Havener served as the lead analyst. Central office staff who provided support include Meghan Kearns and Christine Moritz.

Office of Inspector General

<http://oig.hhs.gov>

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