Department of Health and Human Services

OFFICE OF INSPECTOR GENERAL

THE FOOD AND DRUG ADMINISTRATION'S NATIONAL DRUG CODE DIRECTORY

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EXECUTIVE SUMMARY

OBJECTIVE

To determine (1) whether the Food and Drug Administration's (FDA) National Drug Code Directory (the Directory) is a complete and accurate listing of currently marketed prescription drug products; and (2) if the Directory is not complete or accurate, those factors that contribute to missing or obsolete product listings.

BACKGROUND

Among other requirements, the Drug Listing Act of 1972 requires drug firms to list with FDA prescription drug products manufactured, prepared, propagated, compounded, or processed by them for commercial distribution. Drug products are uniquely identified and reported using a three-segment number, called the National Drug Code (NDC). FDA assigns the first segment and drug firms assign the other two segments. As drug firms introduce a new drug product, or discontinue a product, they must report the complete NDC and associated information to FDA as part of the drug product listing process.

A comprehensive list of drug products supports a variety of compliance activities and health initiatives at FDA and other Federal agencies. Examples of activities and initiatives include recalls of dangerous or tainted drugs, bioterrorism response, drug importation, and NDC barcoding of drug products.

FDA inputs drug product information into a database known as the Drug Registration and Listing System (DRLS). If a drug firm does not list its marketed drug products properly with FDA, they are deemed misbranded and FDA can take enforcement action against the drug firm. At the time of this study, every 3 months FDA extracted a database of all currently listed drug products from the DRLS, known as the Directory. As of February 2005, the Directory included 123,856 prescription drug products listed with unique NDCs.

FDA is currently pursuing changes to facilitate the submission of drug listing information and firm registration information by drug firms and to improve industry compliance with mandatory submission of this information to FDA, including provision of electronic submission capability. These changes warrant revision of existing regulations, and FDA is preparing to publish changes in a proposed rule.

To identify prescription drug products that were missing from the Directory or that were still listed after they were discontinued, we compared the Directory with a private industry database, First DataBank's National Drug Data File Plus™ (First DataBank). To confirm the status of the NDCs identified, we reviewed documents obtained from FDA and surveyed drug firms to determine the market status of the drug products. Further, we examined FDA's processes for drug listing by interviewing FDA staff and reviewing procedural guidelines. The findings in this report reflect the Directory as of February 2005.

FINDINGS

The Directory is incomplete, with an estimated 9,187 prescription drug products missing, primarily due to insufficient reporting by drug firms. For 16 percent of missing NDCs, drug firms confirmed that they did not submit the required FDA forms for listing the drug products. In nearly all of the remaining cases in which drug firms claimed to have submitted listing forms, evidence of submission was not provided or the documentation provided was inconclusive. However, in 9 percent of cases, firms' claims to have submitted forms were corroborated by forms we found in FDA's files. In these cases, FDA had failed to appropriately process the forms.

An estimated 5,150 marketed drug product listings are pending, primarily because drug firms failed to submit complete listing information and because of submission errors. For 94 percent of the products in FDA's pending file, firms failed to provide the information required for listing. Drug firms' most frequent errors were failure to submit labels and insert materials and failure to provide manufacturer information for a product they were repackaging or distributing.

The Directory is not accurate, with an estimated 34,257 drug products no longer on the market or listed in error, primarily because drug firms failed to report drugs taken off the market. Fifty-four percent of inaccurately listed drug products resulted from drug firms' failure to submit forms to notify FDA that the drug was discontinued. An additional 18 percent resulted from firms' assigning new NDCs to existing products and failing to discontinue the old ones. The remaining inaccurately listed drug products were the result of drug firms' going out of business and not reporting product status (13 percent), drug firms' reported unawareness that they had listed the drug product and

consequent failure to update drug product status with FDA (13 percent), and FDA errors (3 percent).

FDA's drug product listing process and lack of oversight contribute to deficiencies in the Directory. FDA's manual process for listing drug products provides opportunities for errors that may cause NDCs to be processed incompletely or incorrectly. Procedural breakdowns are evident by the number of NDCs in the pending file or not listed even though the appropriate listing forms from drug firms were present in FDA's files. Additionally, FDA has neither finalized guidance documents for listing procedures nor established adequate avenues of communication, according to drug firms. Further, the Directory is not updated timely and is cumbersome for firms to use to verify their listings. Inadequacies such as these may deter drug firms from listing drug products or following up to verify listings.

Although FDA is aware that firms fail to submit drug products for listing, FDA staff reported to us that they do not actively pursue information about unlisted drug products. As of August 2005, FDA had not taken enforcement action against any drug firm solely on the basis of its failure to list drug products or update listings, although FDA has added listing failures to charges when taking action against firms for other violations.

RECOMMENDATIONS

FDA should:

- Finalize guidance documents for submission of forms to list drug products,
- Assume greater control over the assignment of NDCs,
- Continue efforts to implement electronic submission of listing forms by drug firms,
- Implement a mechanism to routinely identify omissions and inaccuracies in the Directory,
- Resolve the status of drug product listings in the pending file,
- Enhance communication with drug firms, and
- Identify and take appropriate action against drug firms that consistently fail to list drug products and update information.

AGENCY COMMENTS

FDA concurred with each recommendation and requested access to our data files to follow up on identified problems. In its response, FDA delineated a number of initiatives it expects will improve the Directory's completeness and accuracy, such as conversion to an electronic listing system for use by drug firms. While FDA acknowledged the existence of many missing and inaccurately listed drug products, it stated that our results show a marked decrease in the percentage of missing drug products since 1990. FDA also expressed concerns with the study's methodology, which it believes potentially resulted in our overestimation of the extent of problems with the Directory.

OFFICE OF INSPECTOR GENERAL RESPONSE

We will provide access to our data files so that FDA can follow up on the problems identified in this report.

In response to FDA's concerns with our study methodology, we believe that the methodology was appropriate for the purpose of identifying missing or inaccurate drug products and did not overestimate the extent of problems. We acknowledge the apparent decline in the percentage of missing drug products, and we continue to recommend that FDA implement the actions described to address the remaining issues identified and ensure that the Directory is complete and accurate.

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INTRODUCTION

OBJECTIVE

To determine (1) whether the Food and Drug Administration's (FDA) National Drug Code Directory (the Directory) is a complete and accurate listing of currently marketed prescription drug products; and (2) if the Directory is not complete or accurate, those factors that contribute to missing or obsolete product listings.

BACKGROUND

The Drug Listing Act of 1972 (the Act) requires drug firms engaged in manufacturing, preparation, propagation, compounding, or processing drugs to report all drug products to FDA.[1] Pursuant to the Act and implementing regulations, the process of new drug product reporting, known as "listing," is to occur within 5 days of the establishment's first entry into one of these operations and be updated thereafter twice each year.[2] In addition, certain changes to drug product information, e.g., discontination, must be reported to FDA twice yearly.[3, 4]

Mandatory listing by drug firms promotes FDA's mission to protect the public by ensuring the safety, efficacy, and security of human drug products. Drug products that are not properly listed are considered "misbranded" and the firms that are responsible may be subject to criminal or regulatory action.[5] According to FDA officials, as of August 2005, FDA had not taken any such action against a firm solely on the basis of its failure to list drug products, although it has added listing failures to charges when taking action against firms for other violations.

A comprehensive list of drug products supports a variety of compliance activities and health initiatives at FDA and other Federal agencies, such as recalls of dangerous or tainted drugs, bioterrorism response, and barcoding certain drugs with drug product universal identifiers, known as National Drug Codes (NDC). [6,7]

NDCs uniquely identify each drug product. They were originally developed for outpatient drug reimbursement under Medicare, but were later used for other purposes. Currently, for example, the Centers for Medicare & Medicaid Services uses NDCs to assess compliance with program requirements for participation in the Medicaid Drug Reimbursement and Rebate programs. NDC information is also vital for importation of drug products. Border

agents routinely verify drug product NDCs with FDA before allowing drugs to enter the United States.

National Drug Code Directory

FDA maintains a publicly accessible database of drug manufacturers and drug products called the Directory. As of February 2005, the Directory contained 123,856 drug product listings, each with a unique NDC. The Directory reflects FDA's knowledge of drug products in commercial distribution. The Directory is supposed to include every drug firm that markets prescription, over-the-counter and homeopathic drugs, and an NDC for every such product currently on the market.

The Directory is FDA's inventory of drug facilities and commercially marketed drug products; therefore, it plays a significant role in protecting public health. FDA and others use information in the Directory when they perform many functions, such as inspecting drug facilities, identifying ingredients for marketed drug products, managing drug recalls and withdrawals, dealing with drug shortages, verifying drug imports, identifying medication errors, monitoring adverse drug experiences, and evaluating drug impacts of natural disasters and terrorist threats. In addition, NDCs are almost universally used to identify drug products in pharmaceutical billing and reimbursement systems and in drug information resources.

FDA's system for collecting and maintaining drug product information from firms is known as the Drug Registration and Listing System (DRLS). Drug firms submit their drug products' NDC information to FDA using Forms FDA-2657 or FDA-2658.[8, 9] Once the forms are received, data are entered into the DRLS by staff contracted to perform this function. During calendar year 2004, 15 full-time contract employees processed 19,601 forms from drug firms. A flowchart depicting FDA's drug listing process is included in Appendix A.

A drug product and its associated NDC may reside in one of three databases within the DRLS:

- The DRLS Listed Drug File—currently marketed drug products that were successfully listed; this file is the source of the Directory and, at the time of this study, was extracted every 3 months.
- The DRLS Discontinued Drug File—discontinued drug products that were listed but are no longer on the market as reported by firms or known to FDA.

- The DRLS Pending Drug File—drug products for which the listing process is not complete.[10]

An NDC consists of three numeric segments. The first segment is a labeler code, the second segment is a product code, and the final segment is a package code.[11] While FDA is ultimately responsible for assigning NDCs, it currently only assigns the labeler code segment. The labeler code is the unique identifier for each drug firm and is assigned when the firm registers with FDA.[12] Drug firms assign the product and package code segments of the NDCs. The product code identifies the strength, dosage form, and formulation of the particular product, and the package code identifies the size and type of package. Combining these segments produces a 10-digit number. [13]

Drug Industry Product Databases

The drug industry has developed several commercially available databases listing drug products and associated NDCs. These databases exist primarily to provide users with pricing and use information. One of the more prominent and frequently used commercially available databases is First DataBank's National Drug Data File Plus™, hereafter referred to as First Databank, which is used by both private industry and Government agencies. [14] As with FDA's Directory, First Databank relies almost exclusively upon drug firms to report drug products and their associated NDCs. In contrast to required reporting to FDA, firms voluntarily report to First DataBank; however, First DataBank staff report that they actively pursue information and updates from drug firms.[15]

Past Study of FDA's Drug Databases

A 1991 study by the Office of Inspector General (OIG), "The FDA Prescription Drug File," identified problems with the listing process and inadequacies in the DRLS data files.[16] OIG found that the Directory was neither complete nor totally accurate. An estimated 8,000 products were on the market but not listed and an estimated 1,400 products were inaccurately listed. The OIG report attributed these shortcomings primarily to firms' failures to supply the prerequisite information for listing. Other deficiencies included lack of quality control in DRLS processes, limited procedural guidelines, inadequate systems software, uncertain legal authority, and unclear data requirements for the industry. Recommendations to FDA included clarifying data requirements for industry, developing internal quality control procedures for manual data processing, and ensuring

effective use of a new ORACLE data system developed to support the DRLS.

In response to these recommendations, FDA took steps to strengthen the drug product listing process and to streamline data entry procedures. For example, FDA added automated error checking to the ORACLE data system and implemented procedures to barcode incoming documents to better track listing information received from drug firms. Further, FDA developed a clear set of internal guidelines for processing forms and information. According to FDA officials, associated staffing levels were increased by 52 percent during the next 7 years. However, in subsequent years, the staffing levels have dropped to below pre-1991 levels. In acknowledging the reduction, FDA officials provided no explanation for the decline. The DRLS database has expanded from 39,000 prescription drug products in 1990 to more than 120,000 products in 2005 and the number of listing forms processed each year has more than doubled.

FDA's Proposed Changes to the Listing Process

Although changes in the early 1990s improved the FDA listing process, additional improvements are currently being pursued. For example, FDA is pursuing implementation of electronic submissions of listing information by firms. In 2001, FDA pilot-tested the feasibility of electronic submission of information from firms for listing NDCs and providing updates. According to FDA officials, the pilot project provided valuable lessons as FDA moves toward full implementation. Implementation timeframes were uncertain as of January 2006 when OIG discussed the status of this initiative with FDA. Regulatory changes necessary to implement the system are underway with the expectation that the system will take a few years to become fully operational.

METHODOLOGY

This study compared NDC listings for prescription drug products in the Directory to NDCs in First DataBank as of February 2005. First DataBank was chosen as the basis for the comparison because it is widely used by both private industry and Government agencies and because it was used for the 1991 OIG study. The comparison of the NDCs in the Directory to those in First DataBank served to identify both currently marketed prescription drug products not listed with FDA and discontinued prescription drug products inaccurately listed

with FDA as still on the market. We contacted drug firms to verify the market status of a random sample of missing and possibly discontinued drug products. Further, we obtained drug firms' insights into and experiences with the listing process through a survey. We performed onsite case reviews and observations at FDA to enhance our knowledge of the listing process. (See Appendix B for a detailed description of the methodology.)

This study focused on drug products falling into the following three mutually exclusive groups as of February 2005, after we matched FDA and First DataBank databases:

- Group 1: Missing NDCs—NDCs that were in First Databank, but were not in the Directory or the FDA pending file;
- Group 2: Pending NDCs—NDCs that were in FDA's pending file and in First DataBank, but not in the Directory; and
- Group 3: Discontinued NDCs—NDCs that were in the Directory, but were not in First DataBank.

To adjust match results to exclude NDCs for drug products no longer on the market, we randomly selected samples from each group to verify with the drug firms.

A simple random sample of 100 NDCs was taken from the 13,163 NDCs in Group 1 and a simple random sample of 100 NDCs was taken from the 5,479 NDCs in Group 2, to equal 200 NDCs that were in First DataBank and not listed in the Directory. For these samples, we examined FDA files to determine whether FDA had received the required Form FDA-2657/2658 to list the new drug products or to change information or status for drug products already listed. For the pending NDCs (Group 2), we requested information from FDA to explain why the drug product listings were pending. Additionally, we sent information requests to drug firms to determine whether the products corresponding to each NDC were on the market and whether drug firms submitted the necessary forms to list them. We asked drug firms to provide documentation of their submissions, i.e., a copy of the Form FDA-2657/2658 they had submitted.

For Group 3, we selected a simple random sample of 200 from the 94,682 NDCs to determine the proportion of drugs in the Directory that were discontinued or listed in error. We examined FDA files to determine whether a Form FDA-2657/2658 had been submitted to discontinue the listing. We sent information requests to the drug firms

to find out whether the drug products were on the market and, if not, whether the drug firms had submitted the necessary forms to discontinue the listing (again requesting copies of Forms FDA-2657/2658 submitted).

We calculated estimates by generalizing the results from the sample findings to the respective populations based on a 95-percent confidence interval. Each confidence interval estimated the range of values that was likely to include the population parameter. Upper and lower boundaries of the confidence limits are reported in Appendix C.

When we had questions about information in FDA files from any of the three groups, we contacted FDA staff. They provided clarification or additional information as needed. We also contacted drug firms when we needed clarification or further information.

Data Limitations

Because drug firms are not required to list with First DataBank, that database does not include all drug products from all drug firms. Consequently, our analyses underestimate the number of NDCs missing from the Directory. The extent of underestimation is unknown.

Quality Standards

This study was conducted in accordance with the "Quality Standards for Inspections" issued by the President's Council on Integrity and Efficiency and the Executive Council on Integrity and Efficiency.

FINDINGS

The Directory is incomplete, with an estimated 9,187 prescription drug products missing, primarily due to insufficient reporting by drug firms

The Directory, consisting of 123,856 drug products as of February 2005, is missing an estimated 9,187 drug products that are listed in First DataBank. (See Appendix C for confidence intervals for estimates.) These drug products were on the market and listed in First DataBank, but unlisted with FDA. We found that 28 percent of the 47,814 drug products listed in First DataBank were not listed with FDA. This finding confirms that firms do not always list drug products with FDA, even when they list them with First DataBank.

The timing of the submissions to both First DataBank and the Directory does not appear to have caused the discrepancy. Because drug firms are required to list a drug product with FDA within 5 days of first manufacturing, distributing, or repackaging drugs and to update this information twice each year thereafter, a drug product should rarely be listed with a private database before it is listed with FDA. We checked the length of time drug products were listed in First DataBank and found that more than three-fourths of the drug products missing from the Directory were listed with First DataBank for longer than 1 year, suggesting that they had been on the market for at least that long without being reported to FDA.

Missing drug products primarily result from firms' failure to submit required forms

For an estimated 16 percent of the missing drug products that are currently on the market, drug firms confirmed that they did not submit the appropriate listing forms (see Table 1). Drug firms gave no explanation for not submitting forms. For 28 percent of drug products, drug firms reported submitting forms to FDA; however, they were unable to provide evidence of the submission and no evidence was found in FDA's files. Drug firms reported submitting listings for 46 percent of missing drug products and provided evidence; however, the documentation was insufficient or questionable and, consequently, we were unable to substantiate the claims. For example, some drug product listings were submitted to FDA after our request for data, which was reflected in the documentation submitted to us by the firms. However, we did find evidence of listing in FDA files for 9 percent of unlisted products that are currently on the market.

Table 1: Reasons Drug Products Were Missing From the Directory

Reason	Estimated Percentage	95% Confidence Interval
Firm reported its product was listed and provided evidence of submission, but the evidence was questionable.	46.3	± 12.3
Firm reported its product was listed, but did not provide evidence of submission and no evidence was found in FDA files.	28.4	± 11.1
Firm reported it did not list its drug product.	16.4	± 9.1
Firm reported its product was listed and we found corroborating evidence of submission in FDA files.	9.0	± 5.6

Source: OIG analysis of a sample of missing NDCs for products that are currently on the market.

Some drug firms have never listed their products with FDA even though they have drug products currently on the market

Specifically, we found that 23 drug firms that registered with FDA and have been assigned a labeler code (the portion of the NDC assigned by FDA to designate the firm) had listed drug products in First DataBank but never with FDA. In an extreme case, one firm has listed 1,932 drug products in First DataBank for at least 8 years but has never listed any products with FDA. We also found that nine firms with products listed in First DataBank had labeler codes that had not been assigned by FDA.

An estimated 5,150 marketed drug product listings are pending, primarily because drug firms failed to submit complete listing information and because of submission errors

Drug products in pending status are not in the Directory even though they may be on the market. We found that 94 percent of pending prescription drug products (5,150) at FDA that are listed with First DataBank are currently on the market. This group of drugs should be in the Directory. The primary reasons these drug products were pending were that the drug firms had failed to provide all required information and had made errors in completing the forms. Table 2 shows all the reasons drug product listings were placed in pending status. Many drug products were in the pending file for multiple reasons.

Table 2: Reasons Drug Product Listings Were in the DRLS Pending File

Reason	Percentage of NDCs*	95% Confidence Interval
Firm failed to submit required label and/or insert material.	40.4	± 10.0
Repackager/distributer failed to provide complete and/or accurate manufacturer information on the listing form.	39.4	± 10.0
Manufacturer had not registered and listed the product with FDA when the repackager/distributor submitted its listing.	34.0	± 9.6
Error in form completion or missing information, other than manufacturer information and label.	11.7	± 6.6
Unknown.	2.1	- 1.8 / +5.4**

*Totals more than 100 percent because some drug product listings were pending for more than one reason.
**To adjust for invalid results because of the small number, this confidence interval was calculated with an exact method based on the binomial distribution.

Source: OIG analysis of a sample of pending drug products on the market. Reasons were provided by FDA.

Drug firms' failure to submit the required labels and/or inserts was the reason 40 percent of NDCs remained in the DRLS pending file. Drug firms that repackage and distribute drugs manufactured by other companies are required to assign their own NDCs to the repackaged products and submit Form FDA-2657/2658 with information about the manufacturer and manufacturing site. If the drug product's original manufacturer has not yet listed the product with FDA, FDA will not allow the repackager to list the repackaged product and sends the submission back to the repackager. Many repackagers reported that making sure their submission of Form FDA-2657/2658 arrives at FDA after the manufacturer has listed the original product and obtaining the requisite information, e.g., site registration number, from these manufacturers is problematic. Repackagers/distributors' failure to provide complete and accurate information about the manufacturer was the reason 39 percent of the drug products were in the DRLS pending file. An additional 34 percent were pending because the manufacturer had not listed the original product with FDA. Other errors in submissions accounted for only 12 percent of pending NDCs. The reason for pending status was unknown for 2 percent of drug products sampled.

Lack of followup by drug firms with FDA to verify that drugs have been listed contributes to drug product listings' remaining in the DRLS pending file. Many drug product listings have been in a pending status for years, averaging 26 months as of February 2005. In explaining the status of the pending listings, FDA stated that from 2001 to 2005 it discontinued its follow-up process of alerting firms of deficiencies in their listing submissions. As a result, drug firms only discovered problems with listings after they initiated contact with FDA; after they used FDA's Directory to determine the status of listings; or after a problem arose because a drug product was not in the Directory, e.g., products held at the border because U.S. Customs was unable to verify the listing. Only 41 percent of drug firms surveyed reported routinely verifying drug product listings.

The Directory is not accurate, with an estimated 34,257 drug products no longer on the market or listed in error, primarily because to drug firms failed to report drugs taken off the market

An estimated 36 percent of drug products that were in the Directory and not in First DataBank were no longer on the market or were listed in error. When products are removed from the market, drug firms are required to notify FDA that their product has been discontinued. FDA will remove the drug product from the Directory. Additionally, when firms assign a new NDC to an existing product they are required to notify FDA in accordance with FDA regulations.[17] Drug firms accounted for most inaccuracies by failing to discontinue drug product listings when they removed products from the market, assigned new NDCs, or went out of business. Fifty-four percent of drug products that were no longer on the market were still listed as active because drug firms failed to submit appropriate forms to notify FDA that the drugs were discontinued (see Table 3). Drug firms assigned new NDCs to 18 percent of the drugs in this group and failed to discontinue the old NDC listings. Drug firms no longer in business accounted for an additional 12.5 percent of drug product listings that should have been discontinued. For 12.5 percent of drug products that should not have been in the Directory, the firms reported they had never listed them, although evidence found in FDA's files suggests otherwise. FDA errors, e.g., products listed inappropriately by FDA as prescription drugs, accounted for less than 3 percent of the drug products in our sample.

Table 3: Reasons Drugs No Longer on the Market Remained in the Directory

Reason*	Percentage of NDCs	95% Confidence Interval
Firm failed to notify FDA when the drug was taken off the market.	54.2	± 11.8
Firm assigned a new NDC to the product and failed to notify FDA it had discontinued the old one.	18.1	± 9.1
Firm closed or went out of business and failed to notify FDA.	12.5	± 7.8
Firm was unaware that the NDC was ever listed.	12.5	± 7.8
FDA error.	2.8	-2.5 / +6.9*

*To adjust for invalid results because of the small number, this confidence interval was calculated with an exact method based on the binomial distribution.

Source: OIG analysis of a sample of NDCs no longer on the market.

FDA's internal drug product listing process and lack of oversight contribute to deficiencies in the Directory

Listing drug products and reporting NDCs to FDA is a manual process in which drug firms submit paper forms and data entry clerks manually enter the information into the computer. As with any manual process, substantial procedural controls are required to ensure that paperwork is not misplaced and data are entered timely and correctly. While FDA's listing procedures were strengthened following the 1991 OIG report, the listing process remains an issue. The thousands of pending drug product listings and failed postings at FDA indicate that procedural breakdowns at FDA are occurring and oversight is deficient.

Submission of information on paper forms followed by manual data entry sometimes contributes to procedural breakdowns

FDA's failure to properly process submitted forms caused 9 percent of drug products that were on the market to remain unlisted. In these cases, we found documentation in FDA files that the proper documents were submitted. Additionally, FDA data entry errors caused nearly 3 percent of drug products that should not have been in the listing to appear there. Specifically, drug product listings that should have been placed in the FDA pending file were filed away and not addressed, and NDCs for drug products that are treated as prescription drugs in some States were not listed.

FDA has yet to finalize guidance for listing drug products

Although FDA's guidance for listing products is readily accessible on the Internet, the guidance remains in draft form.[18] The guidance document, "Guidance for Industry: Forms for Registration of Producers of Drugs and Listing of Drugs in Commercial Distribution," which was posted in 2001, may confuse drug firms trying to locate current guidelines because the document's cover states "this guidance document is being distributed for comment purposes only." Moreover, although we found that the draft document reflects the current process, 25 percent of drug firms we surveyed claim FDA's guidance is inadequate.

Avenues of communication are lacking, according to drug firms

To contact FDA staff, drug firms have the option of using mail, telephone, or e-mail. While several surveyed drug firms commented positively on the quality of interactions with FDA staff, stating that FDA staff are helpful, willing to explain, competent, and courteous, many reported that contacting FDA is problematic. Survey responses suggested that either drug firms are unaware of available options for communicating with FDA, or FDA staff response may not be timely. Drug firms reported that when they use the telephone number provided by FDA, they reach a recording requesting that they leave a message and someone will respond. Although FDA staff may respond within a 24-hour period as publicized, some surveyed drug firms report that this callback process frequently leads to "telephone tag," lengthening the time to resolve an issue.

The Directory is not updated timely and is cumbersome for firms to use to verify their listings

As previously mentioned, drug firms' lack of followup to ensure successful listing with FDA contributes to drug product listings' remaining in FDA's pending file. Surveyed firms said that when they do check with FDA to verify a listing, they frequently check FDA's Web site, which gives access to the Directory. While the Directory is readily accessible, several firms raised concerns that it is updated too infrequently, i.e., once every 3 months. Another concern with Web site verification is that NDCs can only be looked up one at a time; thus, checking the firm's listings becomes increasingly cumbersome as the number of listings rises. Some drug firms call FDA to verify individual drug listings or to request printouts they can review; however, this contact can be time-consuming to both FDA and drug firm staff.

FDA provides limited oversight and enforcement to ensure that drug firms list drug products and provide status updates

In 1991, OIG reported that incompleteness and inaccuracies in the Directory were primarily attributable to drug firms' failure to supply requisite information for listing. Despite this finding, FDA staff reported to us that they still do not actively monitor firms to identify unlisted drug products or listings of drug products no longer on the market. They do not currently match the Directory with other drug product listing data sources. Failure to monitor firms' reporting results in some drug firms' completely ignoring listing requirements. As mentioned earlier, one such firm has nearly 2,000 drug products in First DataBank but none in the Directory. As of August 2005, FDA staff reported to us that no regulatory action has been taken thus far against any drug firm solely on the basis of its failure to list drug products or provide updates, although FDA has added listing failures to charges when taking action against firms for other violations.

RECOMMENDATIONS

The results of this review demonstrate that the Directory is neither complete nor accurate. We identified thousands of missing drug products that firms should have listed with FDA and many more drug products inaccurately listed as still on the market. Because drug product listing with FDA is not optional, most omissions and inaccuracies are directly related to drug firms' failure to meet Federal requirements to list their products.

The failure of firms to list drug products with FDA limits the usefulness of the Directory to all who rely on it for timely information about prescription drugs currently on the market. For example, FDA's initiative to prevent medication errors by requiring manufacturers to place NDC barcodes on certain drug products may in turn depend on FDA providing a complete listing of NDCs. The current Directory would inhibit FDA's ability to do this.

FDA should address issues with the drug product listing process to ultimately create a more complete, accurate, and reliable Directory. Specifically, we recommend that FDA:

Finalize Guidance Documents for Submission of Forms To List Drug Products

Because electronic submission of listings will take some time to become operational, FDA should finalize the current draft guidance issued in 2001 and referenced on its Web site. Additionally, any changes to the process based on this report's findings and any action by FDA in response to this report should be included in the finalized document. A review of common submission errors may be helpful for suggesting enhancements to the guidance document.

Assume Greater Control Over the Assignment of NDCs

Were FDA to take more control of the NDC assignment process, e.g., by assigning all parts of NDCs, it might largely prevent NDCs associated with drug products on the market from being omitted from the DRLS and, consequently, the Directory.

Continue Efforts To Implement Electronic Submission of Listing Forms by Firms

Electronic filing of drug registration and listing information will facilitate the timely exchange of information between FDA and firms. The current system, in which drug firms submit Form FDA-2657/2658 and clerks manually enter the information into the system, is labor intensive and time consuming both for drug firms and for FDA. An electronic process

would allow FDA to redirect resources toward other areas of the listing process such as communication with firms.

Implement a Mechanism To Routinely Identify Drug Product Omissions and Inaccuracies in the DRLS and, Subsequently, the Directory

FDA could routinely compare the Directory with other Government databases and commercial databases to identify unlisted or discontinued drug products. Although private industry databases, because of their voluntary nature, will never include all drug products, they provide a readily accessible means of identifying a significant portion of unlisted or discontinued drug products.

Resolve the Status of Drug Product Listings in the DRLS Pending File

The current procedure for following up on deficient submissions should prevent further accumulation in the pending file. However, previous submissions already in the pending file should be resolved with firms and either listed or dropped.

Enhance Communication With Drug Firms To Facilitate Accurate and Complete Reporting of Drug Product Listings

FDA should expand firms' ability to verify submitted drug product listings. Drug firms we surveyed commented frequently on the difficulty they experience when verifying drug listings. To address their concerns, FDA could improve the Web site reporting function to allow drug firms to easily generate a complete listing of their drug product NDCs so it could update the Directory more frequently.

FDA could also provide more timely assistance options for drug firms with questions about submitting data or other problems. Options could include a customer service hotline or a quick-response e-mail address.

Identify and Take Appropriate Action Against Drug Firms That Consistently Fail To List Drug Products and Update Information

Many drug firms fail to comply with listing regulations. The lack of enforcement actions by FDA against drug firms that consistently do not comply provides little incentive for drug firms to complete and submit forms.

AGENCY COMMENTS

FDA concurred with each recommendation and requested access to our data files to follow up on identified problems. In its response, FDA listed a number of initiatives it expects will improve the Directory's completeness and accuracy, such as its planned implementation of an electronic listing system for use by drug firms. While FDA acknowledged the problem of missing and inaccurately listed drug products in its DRLS, it stated that our results show a marked decline in the extent of drug product listing problems. The ratio of missing drug products to the overall number of drug products in the Directory is much lower than reported in our 1990 report.

In its comments, FDA also stated that our study methodology potentially resulted in an overestimation of the extent of problems with the Directory. Concerns included the use of First DataBank as a basis for comparison, sample size, and the exclusion of two groups of NDCs from sampling. Additionally, FDA pointed out that our finding that 36 percent of drug products listed were no longer on the market or were listed in error was not representative of the entire Directory; rather, the finding only applied to the group of NDCs that were in the Directory and not in First DataBank. The full text of FDA's comments is in Appendix D.

OFFICE OF INSPECTOR GENERAL RESPONSE

We will provide access to our data files so that FDA can follow up on the problems identified in this report.

In response to FDA's concerns about our use of First DataBank as a basis for comparison, we agree that the objectives of the Directory and First DataBank differ and that First DataBank is not intended to be a complete listing of all drugs currently on the market. However, a more complete listing would likely have identified a greater number of drug products that are on the market and not listed in the Directory. In other words, use of First DataBank likely resulted in an underestimation of the extent of missing NDCs.

Regarding the second concern, while a larger sample may have reduced the confidence intervals around the estimates, the sample sizes were sufficient to accurately quantify the problems cited. These estimates were calculated using appropriate sampling techniques and do not lead either to underestimation or to overestimation.

FDA's third concern was with our exclusion of two groups of NDCs from sampling. These excluded groups contain the NDCs in both the Directory and First DataBank and those NDCs pending with FDA. The purpose of this study was not to provide an overall error rate, but rather to identify missing and inaccurate NDCs. Our sampling methodology was appropriate for this purpose. The data presented in this report pertain only to the sampled groups and identify missing and inaccurate drug products in FDA's databases.

With regard to FDA's comment that our finding concerning the 36 percent of drug products was not representative of the entire Directory, we clarified the finding's wording in the report.

We acknowledge the apparent decline in the percentage of missing drug products, and we continue to recommend that FDA implement the actions described to address the remaining issues identified and ensure that the Directory is complete and accurate.

ENDNOTES

[1] Food, Drug and Cosmetic Act, §§ 510(j)(1) and 510(b).

[2] 21 CFR § 207.21(a)(b) (2005).

[3] Firms are required to submit updates every June and December.

[4] 21 CFR § 207.21(b) (2005).

[5] Food, Drug and Cosmetic Act, §§ 502, 301(p), and 303.

[6] In 2004, FDA issued a final rule requiring, among other things, prescription drug products to have barcodes that contain NDCs. As a consequence, entities that develop systems to utilize barcodes will require a complete electronic listing of NDCs, which FDA has committed to providing. An incomplete Directory may lessen the usefulness of barcoding and reduce its intended impact as a tool to reduce medication error in health care settings.

[7] Bar Code Label Requirements for Human Drug Products and Biological Products; Final Rule, 69 Federal Register 9120, February 26, 2004.

[8] Form FDA-2657 (the Drug Product Listing Form) is used by drug firms for initial listing of all information for all drugs in commercial distribution, may be used by private-label distributors that elect to submit information directly to FDA, and is used to update information on currently listed drug products. Form FDA-2658 (the Registered Establishment's Report of Private Label Distributors) is used by drug firms to list information for private-label distributors that do not elect to submit listing information directly to FDA.

[9] 21 CFR § 207.22(b) (2005).

[10] The pending drug product file contains 32,418 NDCs for products that have been submitted for listing and need corrections or additional information. The discontinued drug product file contains 62,250 NDCs for products that were discontinued and are no longer on the market.

[11] 21 CFR § 207.35(b) (2005).

[12] For this report, the term "drug firms" represents not only drug manufacturers, but also relabelers, distributors, and repackagers of drug products.

[13] Some Government agencies display NDCs in an 11-digit format that includes a 5-digit labeler code, a 4-digit product code, and a 2-digit package code. FDA uses a 10-digit code that is configured as 4-4-2, 5-3-2, or 5-4-1 (labeler code-product code-package code).

[14] First DataBank, Knowledge Bases, National Drug Data File Plus (2004). Available online at http://www.firstdatabank.com/knowledge_bases /nddf_plus/. Accessed May 2005.

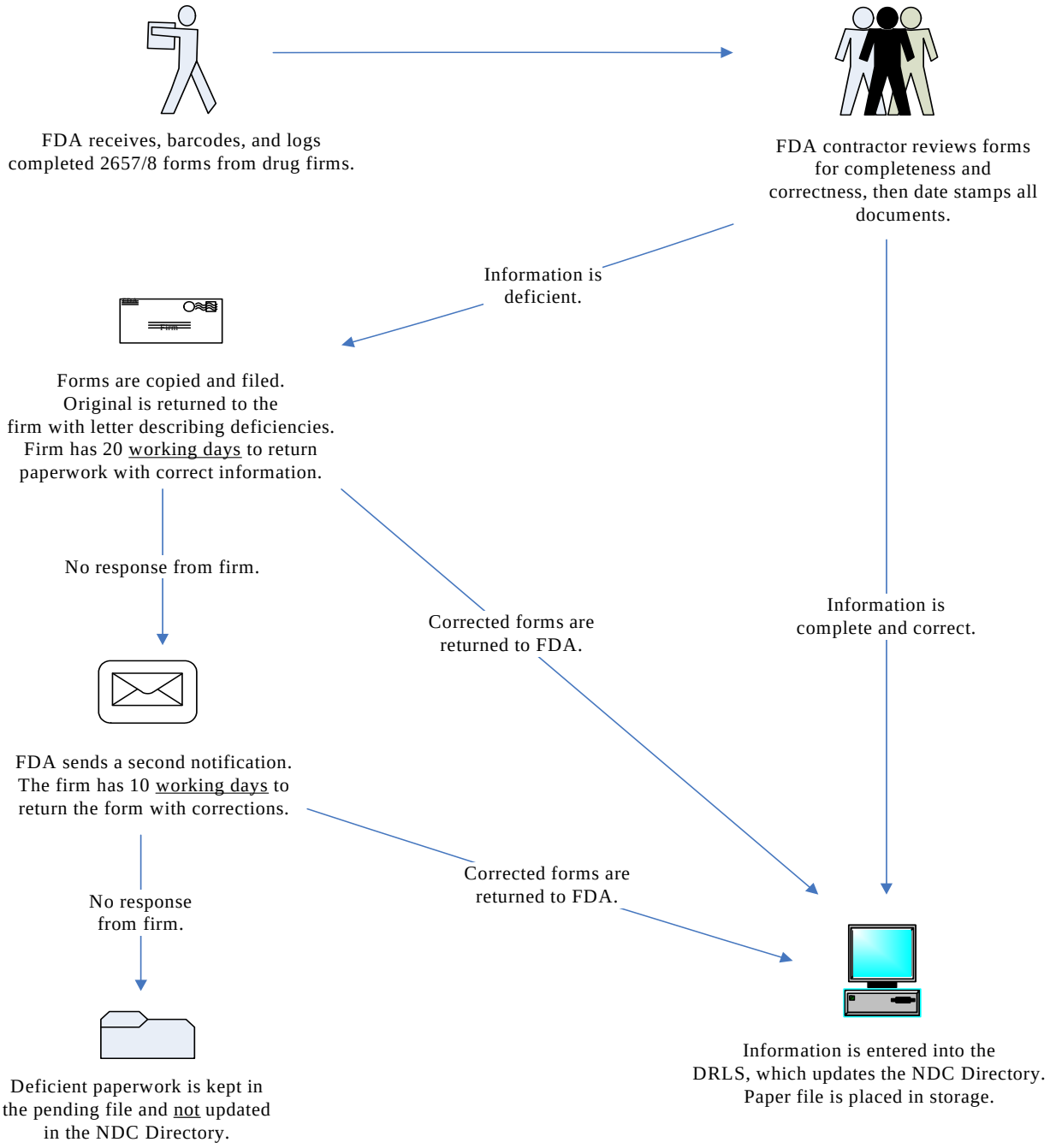
[15] May and July 2005: Telephone interviews with First DataBank staff.

[16] Department of Health and Human Services, Office of Inspector General, "The FDA Prescription Drug File," OEI-03-90-02300, November 1991.

[17] 21 CFR § 207.21(b) (2005).

[18] Available online at http://www.fda.gov/cder/drls/default.htm. Accessed June 15, 2005.

FDA's Current Drug Listing Process



Source: OIG description of FDA's listing process based on interviews with FDA staff and observations of FDA's contractors.

Detailed Methodology

This study relied on multiple data sources and methods. Sources included Food and Drug Administration (FDA), drug firms, and First DataBank. This appendix provides a detailed description of data sources, sample selection, and data collection procedures.

Data Sources

Databases

Databases we used for this study were FDA's Drug Registration and Listing System (DRLS) and First DataBank's National Drug Data File Plus™ (hereafter referred to as First DataBank).

The FDA Drug Registration and Listing System The DRLS consists of the listed drug file or National Drug Code (NDC) Directory, the Pending Drug File, and the Discontinued Drug file. The FDA DRLS files we used were downloaded on and current as of February 11, 2005.

a. *The DRLS Listed Drug File—the "Directory"* The Directory contains all prescription drugs, selected over-the-counter (OTC) drugs, and homeopathic drugs. This study was limited to prescription drugs. The Directory contained a listing of 123,856 NDCs for 57,035 prescription drug products.[1]

b. *The DRLS Pending File* The Pending File contains NDCs submitted by drug firms that were not listed in the Directory because of deficiencies in the submission (i.e., incomplete or incorrect information). The Pending File contained 32,418 NDCs for 13,160 prescription drug products.

c. *The DRLS Discontinued File* The Discontinued File contains NDCs for prescription drugs that are no longer on the market as reported by drug firms. The Discontinued File contained 62,250 NDCs for 38,463 prescription drug products.

First DataBank First DataBank is a private, commercially available database that provides descriptive and pricing information for prescription drugs, OTC drugs, herbal remedies, and dietary supplements. We included only the prescription drugs for this study. The First

[1] Each product may have multiple NDCs because of multiple package codes.

DataBank file we used was downloaded and current as of February 25, 2005, and contained 47,814 NDCs for 24,850 prescription drug products.

Documentary Evidence

We reviewed the following documents:

1. FDA's Guidance For Industry: Forms for Registration of Producers of Drugs and Listing of Drugs in Commercial Distribution (Draft Guidance);
2. Guidance manual provided to FDA contractors responsible for responding to drug listing questions, processing drug registration forms, and posting entries to list drugs in the Directory;
3. Letter templates to inform drug firms of deficiencies in listing submissions; and
4. Samples of listing submissions.

We also reviewed copies of Form FDA-2657/2658 that were submitted by drug firms to list or update the status of NDCs. We obtained copies of forms from FDA files and from drug firms. We compared forms obtained from FDA files with those submitted by drug firms and with information in the Directory.

Interviews

We conducted interviews with FDA staff in May 2005. These interviews provided information about the listing procedures used to process documents received from drug firms. FDA staff described the procedures they follow when drug listing submissions are incomplete or inaccurate.

Information Requests

We sent information request forms to drug firms asking if the NDC in our sample was associated with their respective firm, if the product was still on the market, if they submitted drug listing forms for the NDC and, in cases where the product was no longer on the market, whether they submitted forms to discontinue the listing. If a drug firm reported it had not submitted forms to list or discontinue an NDC, we requested a reason. If the firm reported that it had submitted forms, we requested supporting documentation.

Firm Surveys

Our survey asked firms about difficulties in listing NDCs, their perceptions of the adequacy of guidance provided by FDA, whether and how they verify that their NDCs are listed, if they ever needed to resubmit information because of deficiencies, and how they learned of a need to resubmit material(s).

Data Cleaning

Some cleaning of the Directory, the FDA Pending File, and First DataBank files was necessary. We eliminated records for nonprescription drugs and invalid or incomplete NDCs from the Directory and the FDA Pending File. We eliminated records for discontinued NDCs, those with invalid or incomplete NDCs, and all nonprescription drug products from First DataBank.

The NDC variable in First DataBank is a segmented 11-digit number, rather than a segmented 10-digit number as in FDA's Directory. To compare the Directory with First DataBank, we had to replicate First DataBank's NDC format. In both databases the NDC code is made up of a combination of a labeler code, a product code, and a package code. However, FDA's NDC format is a 3-segment number that allows for various combinations of segment lengths (4-4-2, 5-3-2, 5-4-1) as long as the result is a 10-digit number. First DataBank's format forces a consistent 5-4-2 combination. We added zeroes where necessary to the front of segments and combined the three segments to conform to the 5-4-2 format used by First DataBank.

Sample Selection

We sampled 400 NDCs to estimate the proportion missing from the Directory and the proportion that should not be in the Directory. We did this to verify which NDCs were still on the market.

We matched the Directory and FDA Pending File with First DataBank to determine unlisted NDCs that were in First DataBank, and NDCs in the Directory but not listed in First DataBank. Table B1 provides more information about our population and samples.

- We randomly selected 200 NDCs from the 18,664 products listed in First DataBank but not in the Directory. We selected 100 NDCs missing from all DRLS files and 100 present in the FDA Pending file but not the Directory.
- We randomly selected 200 NDCs from the 94,682 products listed in the Directory but not in First DataBank.

Table B1: Source Databases and Sample Size by Category		
Number of Records in Database		
FDA Directory	123,856	
First DataBank	47,814	
FDA Pending File	32,418	
Number of Records in Population		
	Population Size	**Sampled**
Products in Directory but NOT First DataBank	94,682	200
Products in First DataBank but NOT Directory	13,163	100
Products in First DataBank and FDA Pending File	5,479	100

Source: OIG matching of FDA Directory and Pending file with First DataBank.

Data Collection

FDA Files

We went onsite at FDA to collect available physical files for each NDC in our three samples. FDA staff also searched files for forms we were unable to locate.

Pending NDC Information

FDA provided a DRLS database printout in Microsoft Excel format of the reasons listings were pending for our sample of 100 NDCs in the Pending File and First DataBank.

Firm Survey

There were 173 different drug firms associated with the 400 sampled NDCs. We sent surveys to 172 of the 173 drug firms.[2] To respond to the questions, drug firms needed to have experience with listing NDCs. Fourteen drug firms were classified as ineligible for a variety of reasons (see Table B2). Five drug firms refused to respond to the survey. The final survey reponse rate was 97 percent as shown in Table B2.

[2] We determined that one firm was ineligible to respond and therefore did not send a survey to that firm.

Table B2: Drug Firm Survey Response	
Group	**Number**
Drug firms with products in sample	173
No survey sent; identified as unable to respond for a valid reason	1
Ineligible: Out of business	9
Ineligible: Do not complete their own forms	3
Ineligible: No longer own pharmaceutical division of business	2
Final sample size	158
	Response
Refused to respond	5
Surveys completed	153
Response rate	97%

Source: OIG analysis of surveys mailed to and returned by drug firms.

Firm Information Request

We sent 399 information request documents to the 172 drug firms with NDCs in our sample.[3] We did not receive 10 responses from 9 drug firms that were no longer in business. All were in the sample of NDCs in FDA and not First DataBank. We coded these as "no longer on the market" and grouped them with other NDCs that should have been discontinued. (See Table B3.)

Analysis of Quantitative Data

Firms' responses to the information requests were used to code whether the products were on the market and whether the drug firms reported they had submitted forms to list or delist NDCs. Reasons NDCs were pending were coded from information provided by FDA.

Drug firms were coded as "out of business, products off the market" when: (1) the information request was returned by the Postal Service, (2) an exhaustive Internet search for information about the firm produced no results, and (3) we verified the firm's last registration date and other relevant information with FDA.

[3] Some firms had more than one NDC in our sample and received multiple information request forms.

Table B3: Information Request Response	
Sample: Records Not in FDA's Directory but Listed in First DataBank	
Initial sample	100
Ineligible: products were OTC drugs	3
Final sample	97
Number of responses	96
Response rate	99%
Sample: Records in FDA Pending File and Listed in First DataBank	
Initial sample	100
Number of responses	100
Response rate	100%
Sample: Records in Directory but Not in First DataBank	
Initial sample	200
Information requests received from drug firms	189
No response (firm out of business and drug off market)	10
Number of responses	199
Response rate	100%

Source: OIG Analysis of information requests sent to and received by drug firms.

Extrapolating Sample Conclusions to the Population

Estimates generalizing the results from the sample findings to the respective populations were based on a 95-percent confidence interval. Each confidence interval estimated the range of values which were likely to include the population parameter (which is unknown). The upper and lower boundaries of the confidence limits are reported. (See Appendix C.)

Confidence Intervals

Table C1: NDCs on the Market, Not in the Directory, but Listed in First DataBank
Population: 13,163
Number in Sample: 96

Group	Percentage (Number) in Group	95% Confidence Interval for Percentage (Number) on the Market	
		Lower	Upper
NDCs on the Market and Not in the Directory (Number in parentheses below percentage)	69.8 (9,187)	60.5 (7,960)	79.1 (10,413)
Subgroups of NDCs on the Market and Not in the Directory (Analysis of 67 NDCs that were in this group, representing 69.8% of the sample of 96)			
Firm reported listing and provided unsubstantiated evidence	46.3	34.0	58.5
Firm reported listing but did not provide evidence; none found in FDA files	28.4	17.3	39.4
Firm admittedly did not list	16.4	7.3	25.4
Firm reported listing; and evidence found in FDA files*	9.0	3.4	18.5

*To adjust for invalid results because of the small number (negative number on lower confidence interval), this confidence interval was calculated with an exact method based on the binomial distribution.

Table C2: NDCs on the Market and Pending and Reasons Pending
Population: 5,479
Number in Sample: 100

Group	Percentage (number) in Group	95% Confidence Interval for Percentage (Number) on the Market	
		Lower	Upper
NDCs Not in Directory, in FDA Pending File, and on the Market	94.0	89.3	98.7
(Number in parentheses below percentage)	(5,150)	(4,893)	(5,407)
Reasons Pending Subgroups of NDCs Not in Directory, in FDA Pending File, and on the Market (Analysis of 94 NDCs that were in this group, representing 94% of sample of 100)			
Firm failed to provide label and/or package insert	40.4	30.4	50.4
Firm submitted incorrect manufacturer information	39.4	29.4	49.3
Manufacturer has not listed NDC	34.0	24.4	43.7
Other error on the form	11.7	5.1	18.3
Unknown*	2.1	0.3	7.5

*To adjust for invalid results because of the small number (negative number on lower confidence interval), this confidence interval was calculated with an exact method based on the binomial distribution.

Table C3: NDCs Not on the Market, Not in First DataBank, but Listed With FDA
Population: 94,682
Number in Sample: 199

Group	Percentage (Number) in Group	95% Confidence Interval for Percentage (Number) on the Market	
		Lower	Upper
NDCs Not on the Market, Listed in the Directory	36.2	29.5	42.9
(Number in parentheses below percentage)	(34,257)	(27,887)	(40,626)
Subgroups of NDCs Not on the Market, Listed in the Directory (Analysis of 72 NDCs that were in this group, representing 36.2% of the sample of 199)			
Firm failed to delist discontinued product	54.2	42.4	66.0
Firm failed to delist old NDC when new NDC was assigned	18.1	9.0	27.2
Firm no longer in business and did not discontinue NDCs	12.5	4.7	20.3
Firm was unaware of listing	12.5	4.7	20.3
FDA error*	2.8	0.3	9.7

*To adjust for invalid results because of the small number (negative number on lower confidence interval), this confidence interval was calculated with an exact method based on the binomial distribution.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

DATE:

TO: Inspector General

FROM: Acting Commissioner of Food and Drugs

SUBJECT: FDA's Comments on OIG Draft Report: "The Food and Drug Administration's National Drug Code Directory," OEI-06-05-00060

Thank you for the opportunity to review and comment on the Draft Report: "The Food and Drug Administration's National Drug Code Directory," OEI-06-05-00060. The Food and Drug Administration's comments are in the attachment.

If you need additional information, please contact Regina Ledesma at (301) 827-1223.

Andrew C. von Eschenbach, M.D.

Attachments

FDA's COMMENTS ON THE
OIG DRAFT REPORT "THE FOOD AND DRUG ADMINISTRATION'S NATIONAL DRUG CODE DIRECTORY," OEI-06-05-00060

General Comments

We generally agree with the findings and recommendations in the OIG draft report. We are pleased that the OIG has recognized the utility of the Food and Drug Administration's (FDA) Drug Registration and Listing System (DRLS) database by returning for another audit of its procedures and accuracy.

We note that the OIG draft report focuses on analysis of the prescription drug component of the DRLS database and the consequent National Drug Code (NDC) Directory, which is derived from that file and made publicly available. We agree that ensuring the accuracy of the NDC and drug product listing information is important, particularly for prescription drugs. To that end, in addition to providing these comments, we also request access to the original data files utilized by OIG in this audit, so we can follow-up on some of the specific problems they have identified.

We are pleased that the draft OIG report recognizes that FDA is aware of these problems and is working to resolve them, within existing budgetary and regulatory constraints. We recognize that the deficiencies attributable to FDA have occurred over several years of budgetary constraints and concomitant rapid expansion of the numbers and types of drug products on the market. At the time of the prior 1990 audit, for example, the DRLS database contained 39,000 prescription drug products, while in this 2005 audit it contained 123,856 prescription drug products.

We agree, generally, with the OIG finding that a number of marketed drugs are not included in the DRLS database. However, FDA believes that because of limitations in some of the study design elements, including using the First DataBank file for comparison, the audit potentially overestimates the extent of the problem. For example:

- The objectives of the two databases are quite different. The First DataBank data file is established for commercial use, primarily in providing price information and adjudicating drug reimbursement claims. The purpose of the DRLS database is to identify all marketed drugs and their ingredients, manufacturers, and certain other information about marketed drugs. The purpose of the NDC Directory is to provide public access to NDC and drug listing information for all marketed prescription drug products that are properly listed.

- The audit used a very small sample size of drug products that were verified through contact with drug firms.

- The audit sampled only three of the five groups of drug products in the matched databases to develop estimates of percent of drug products on the market. The decision not to sample drug products that are listed in both the NDC Directory and First

DataBank, and the decision not to sample drug products that are pending in DRLS and not included in First DataBank, may also influence the accuracy of the outcome.

In addition to the design issues mentioned above, we would like to note the following:

- The statement that "The Directory is not accurate, with an estimated 36 percent of drug products no longer on the market or listed in error..." is inaccurate in that 36 percent is the estimate pertaining only to those drug products in the DRLS Listed database that did not match to the First DataBank file. When considering the entire DRLS Listed database, the correct percentage is 28 percent.

- The NDC Directory is now updated monthly, rather than quarterly. We hope that will help to improve the Directory's accuracy, completeness, and utility.

Notwithstanding these database and design issues, FDA notes that the study still identifies a significant improvement in reducing the percentage of products that are missing from the DRLS database when compared to the findings of the 1990 audit. Although we acknowledge that these improvements are partially offset by a concomitant increase in the number of drug products included in the database that are no longer on the market, even when adjusted to account for the increase in the over-inclusion of discontinued drugs, the audit still shows a significant reduction in the percentage of omissions from the DRLS database since 1990. This reduction reflects intensive efforts by FDA (in cooperation with industry) to improve the accuracy of the DRLS database for prescription drug products, despite rapidly increasing numbers of drug products on the market.

Moreover, although the DRLS database and the NDC Directory include large numbers of drug products that are now off the market, they do provide information for about 91% of drug products on the market, which is the primary consumer concern. The Agency believes that inclusion of off-market drug products in the database and the Directory is an important issue but less problematic from a public health/regulatory perspective than the omission of marketed drug products.

As noted above, continued inclusion in the database of drugs that are no longer marketed results primarily from failure of drug firms to meet the statutory and regulatory requirements to notify FDA of discontinuation of their drug products, or of changes in NDC numbers for their marketed products. In the past, FDA has mailed Compliance Verification Reports (CVRs) to firms each year to assist and induce them to update their drug listing information. CVRs are computer printouts generated from the drug file and mailed to drug firms. Each report contains a particular firm's product data as it appears in the file. The firm's responsibility is to verify the information and mail the report back to FDA, along with additional data on new, changed, or discontinued products. The use of these reports was discontinued in 2000 due to the extensive resource demands required to process them, and is likely a contributory cause of the increase in inaccurate drug product listings. As noted below in response to Recommendations No. 2 and 3, the conversion to an electronic listing system and future proposed rule are expected to improve DRLS database accuracy, including better verification of marketing status.

In addition to the comments above, our specific responses to the audit recommendations are described below:

OIG Recommendation

1. Finalize Guidance Documents for Submissions of Forms To List Drug Products.

FDA Comment

We concur. FDA is in the process of preparing updates of these guidances and instructions in conjunction with implementation of new electronic registration and listing systems.

OIG Recommendation

2. Assume Greater Control Over the Assignment of NDCs.

FDA Comment

We concur. FDA is preparing a proposed rule that will clarify listing requirements and enhance control of the drug establishment registration and drug product listing processes and improve data accuracy and completeness. Under the proposed rule, FDA would assign the NDC number to newly listed drugs and would take other steps to minimize the use of inaccurate NDC numbers.

OIG Recommendation

3. Continue Efforts to Implement Electronic Submission of Listing Forms by Firms.

FDA Comment

We concur. FDA is in the process of developing and implementing new electronic drug establishment registration and drug product listing systems. This will greatly facilitate these processes for both FDA and industry, reducing duplicative data entry, data errors, and need for data entry resources.

OIG Recommendation

4. Implement a Mechanism To Routinely Identify Drug Product Omissions and Inaccuracies in the DRLS and, Subsequently, the Directory.

FDA Comment

We concur. FDA's new electronic listing system will be linked with electronic submission of content of labeling information, and it will extract listing information directly from the electronic labeling. This will greatly reduce industry burden, reduce data entry errors, and assure that listing information matches that on the drug product labeling. FDA has established working relationships with the Center for Medicare and Medicaid Services (CMS) regarding NDC and listing information and is already working with CMS to facilitate updating drug product listing information.

OIG Recommendation

5. Resolve the Status of Drug Product Listings in the DRLS Pending File.

FDA Comment

We concur. FDA will address these issues during implementation of the new electronic listing system.

OIG Recommendation

6. Enhance Communication With Drug Firms To Facilitate Accurate and Complete Reporting of Drug Product Listings.

FDA Comment

We concur. FDA is developing an industry-relations program in conjunction with implementation of the new electronic registration and listing systems. Additionally, as described above, drug product listing will be linked to electronic submission of content of labeling information, which will greatly ease the burden of the listing process for industry.

OIG Recommendation

7. Identify and Take Appropriate Action Against Drug Firms That Consistently Fail To List Drug Products and Update Information.

FDA Comment

We concur. FDA will be more aggressive in identifying violative firms and in taking appropriate compliance actions.

FDA's Center for Drug Evaluation and Research (CDER) acknowledges the assistance that the OIG has provided in performing this audit of the DRLS data systems, which assists in identifying problems, evaluating accuracy and quality control, and identifying specific needs for resources. If you need additional information, please contact Dr. John Gardner at 301-827-8917.

ACKNOWLEDGMENTS

This report was prepared under the direction of Judith V. Tyler, Regional Inspector General for Evaluation and Inspections in the Dallas Regional Office, and Kevin Golladay, Deputy Regional Inspector General. Other principal Office of Evaluation and Inspections staff who contributed include:

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