Department of Health and Human Services

OFFICE OF INSPECTOR GENERAL

THE FOOD AND DRUG ADMINISTRATION'S GENERIC DRUG REVIEW PROCESS

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EXECUTIVE SUMMARY

OBJECTIVES

1. To determine the percentage of new (i.e., original) generic drug applications approved, tentatively approved, or disapproved by the Food and Drug Administration (FDA) in 2006.
2. To determine the extent to which FDA reviewed original generic drug applications within 180 days in 2006.
3. To identify factors that affected review times for original and amended generic drug applications in 2006.

BACKGROUND

Pharmaceutical companies must submit Abbreviated New Drug Applications (ANDA) to FDA's Office of Generic Drugs (OGD) and receive FDA's approval before marketing new generic drugs. Three OGD divisions review all ANDAs: Chemistry, Bioequivalence, and Labeling. OGD's Microbiology division also reviews some ANDAs. In addition, OGD may consult with other FDA offices during ANDA reviews. All OGD divisions involved in the ANDA review contribute to approval, but disapproval is primarily determined by Chemistry. According to FDA, almost all original ANDAs contain Chemistry deficiencies and are disapproved.

OGD generally follows a first-in, first-reviewed policy for ANDAs. However, when Chemistry identifies no deficiencies in an ANDA (i.e., the ANDA is approvable by Chemistry), the other divisions assign high priority to the ANDA's review. Pursuant to FDA policy, divisions should also assign high priority to ANDAs with minor deficiencies. In addition, some ANDA consults are assigned high priority.

FDA's timeliness in approving generic drugs has recently been a topic of scrutiny by both Congress and the media. Federal law requires that FDA approve, tentatively approve, or disapprove original ANDAs within 180 days of receipt.

We examined review times for 989 original ANDAs under review during 2006. We also surveyed OGD division reviewers assigned to a sample of 105 ANDAs with review times greater than 180 days in at least one division. Finally, we conducted structured interviews with OGD officials to determine factors affecting ANDA review times.

FINDINGS

The Food and Drug Administration approved or tentatively approved 4 percent of original Abbreviated New Drug Applications under review in 2006; the remaining 96 percent did not meet review standards and were disapproved. FDA approved 1 percent and tentatively approved 3 percent of original ANDAs under review in 2006. FDA disapproved 96 percent of original ANDAs under review in 2006 because they contained Chemistry deficiencies.

The Food and Drug Administration exceeded the 180-day review requirement for nearly half of original Abbreviated New Drug Applications under review in 2006 because Chemistry reviews exceeded 180 days. In 2006, Chemistry did not review 46 percent of original ANDAs within 180 days as required by Federal law. For ANDAs taking more than 180 days for review, the median review time was 217 days. Because almost all of these original ANDAs contained Chemistry deficiencies, Chemistry's delay in reviewing these ANDAs resulted in FDA's delay in disapproving them, regardless of the timeliness of the other divisions' reviews.

Microbiology, Bioequivalence, and Labeling reviews of original Abbreviated New Drug Applications generally exceeded 180 days in 2006. In 2006, the percentages of ANDAs with review times exceeding 180 days were 76 percent in Microbiology, 58 percent in Bioequivalence, and 56 percent in Labeling. For ANDAs taking more than 180 days to review, median review times were 361 days in Microbiology, 287 days in Bioequivalence, and 277 days in Labeling.

Nearly 70 percent of sampled division reviews exceeding 180 days did not begin before the 180-day review periods expired. In a sample of 105 ANDAs with review times exceeding 180 days, reviews for 69 percent did not begin within 180 days. Thus, the 180-day periods passed before division reviews began in most of the sample.

The Food and Drug Administration's prioritization practices affect Abbreviated New Drug Application review times. FDA prioritization practices contribute to longer review times for ANDAs that are close to approval.

RECOMMENDATIONS

We found that FDA disapproved most original ANDAs under review in 2006 because they did not meet FDA review standards. Nearly half of Chemistry review times exceeded the 180 days required by Federal law. Moreover, many review times in other OGD divisions exceeded 180 days. In addition, for a sample of ANDA reviews exceeding 180 days, most reviews did not begin before the 180-day period expired. Finally, we found that FDA prioritization practices affect ANDA review times.

The ANDA submissions have increased at more than double the rate of review resources in the last 5 years. To better manage FDA's current ANDA review resources and potentially improve ANDA review times, we recommend that FDA:

Identify common original Abbreviated New Drug Application deficiencies and offer more guidance to industry to decrease the percentage disapproved.

Increase the percentage of original Abbreviated New Drug Applications reviewed by all divisions within 180 days.

Identify new prioritization practices to reduce review times for Abbreviated New Drug Applications close to approval.

AGENCY COMMENTS

In its comments to the draft report, FDA noted that it has already identified portions of the primary recommendations and is implementing process improvements that are the same as or similar to the recommendations. Specifically, FDA agreed with our first recommendation but did not indicate whether it concurred with the two additional recommendations. However, FDA has taken actions that address our recommendations by providing guidance to assist industry in submitting more easily reviewed applications, developing a focused hiring program to increase staff and decrease review times, and prioritizing some ANDAs based on potential market entry date.

We ask that, in its final management decision, FDA more clearly indicate whether it concurs with each of our recommendations.

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BACKGROUND

A generic drug is the same as a reference-listed (i.e., brand name) drug with respect to conditions of use, active ingredient(s), route of administration, dosage form, strength, and labeling.[1] In addition, the generic drug must be bioequivalent to (i.e., perform in the same manner as) the brand name drug.

A generic drug that is therapeutically equivalent is expected to have the same clinical effect and safety profile as the brand name drug when administered under the conditions specified in the labeling. If generic drugs are determined to be therapeutically equivalent, physicians and pharmacists can substitute them for brand name drugs.

Generic drug applications are referred to as Abbreviated New Drug Applications (ANDA).[2] Pharmaceutical companies must submit ANDAs and receive FDA's approval before marketing new generic drugs.[3]

[1] 21 U.S.C. § 355(j)(2) (§ 505(j)(2) of the Federal Food, Drug, and Cosmetic Act); 21 CFR §§ 314.92 and 314.105(c). Some differences between generic and brand name drugs are permitted under 21 U.S.C. § 355(j)(2). See also "Abbreviated New Drug Application (ANDA) Process for Generic Drugs," Center for Drug Evaluation and Research. Available online at http://www.fda.gov/cder/regulatory/applications/anda.htm. Accessed on November 29, 2007.

[2] The term "abbreviated" is used because FDA does not require generic drug manufacturers to submit the clinical studies necessary for brand name drug applications. Instead, the ANDA must demonstrate that the generic drug is the same as a brand name drug.

[3] 21 CFR § 314.105(d).

FDA's timeliness in approving generic drugs has recently been a topic of scrutiny by both Congress and the media.[4] [5] [6] Federal law requires that FDA approve or disapprove ANDAs within 180 days of receipt.[7]

Abbreviated New Drug Application Review Components

Three divisions within FDA's Center for Drug Evaluation and Research (CDER), Office of Generic Drugs (OGD), review all ANDAs: the Division of Bioequivalence (Bioequivalence), the Division of Chemistry (Chemistry), and the Division of Labeling and Program Support (Labeling).[8] [9] In addition, the Microbiology team (Microbiology) reviews some ANDAs.[10]

Other offices within CDER also review ANDAs in certain instances. For example, safety evaluations of inactive ingredients, labeling and bioequivalence protocol reviews, and statistical reviews of bioequivalence studies require OGD to consult other offices within CDER. According to OGD officials, OGD typically sends requests for such reviews (i.e., consults) to the CDER's Office of New Drugs because it has expertise in these areas. CDER policy provides timeframes for

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[4] "The Generic Drug Maze: Speeding Access to Affordable, Life Saving Drugs." Hearing of the United States Senate Special Committee on Aging. July 20, 2006. Available online at http://aging.senate.gov/hearing_detail.cfm?id=270735&. Accesssed on July 24, 2007.

[5] "Appropriations for the Food and Drug Administration." Hearing of the United States House of Representatives Appropriations Committee, Agriculture, Rural Development, Food and Drug Administration and Related Agencies Subcommittee. February 16, 2006.

[6] Kaufman, Marc. "Generic Drugs Hit Backlog at FDA." Washington Post. February 4, 2006, p. A01. Available online at http://www.washingtonpost.com/wp-dyn/content/article/2006/02/03/AR2006020302598.html. Accesssed on July 25, 2007.

[7] 21 U.S.C. § 355(j)(5)(A); 21 CFR § 314.101(f)(2). An approval becomes effective on the date of the issuance of the approval letter, except for certain approvals that have delayed effective dates. An approval with a delayed effective date is tentative and does not become final until the effective date. 21 CFR § 314.105(d).

[8] A CDER organizational chart is available online at http://www.fda.gov/cder/cderorg.htm. CDER provides general information on the ANDA review process online at http://www.fda.gov/cder/ogd/. CDER's "Manuals of Policies and Procedures" (MaPP) provide official instructions to CDER staff on the drug review process. MaPP Chapter 5200 applies to OGD and is available online at http://www.fda.gov/cder/mapp.htm. Accesssed on January 3, 2008.

[9] In addition, the Office of Compliance evaluates the generic drug's manufacturing, packaging, and testing facilities to determine whether they meet current Good Manufacturing Practices pursuant to 21 CFR § 211.

[10] Microbiology reviews drugs administered as injections, inhalations, or solutions to ensure their sterility. The Microbiology staff is officially housed within the Immediate Office of the OGD Director. When referring to OGD divisions throughout this report, Microbiology is included.

OGD to receive consult results from other CDER offices.[11] Policy timeframes range from 15 to 90 days, based on the priority of the consult. A consult's priority is based, in part, on how close the ANDA is to approval.

Abbreviated New Drug Application Review Process

OGD generally employs CDER's first-in, first-reviewed policy for ANDAs.[12] However, OGD grants expedited reviews of ANDAs in special circumstances.[13]

When an applicant submits an original ANDA, OGD first conducts a review to determine whether the application is sufficiently complete to permit a substantive review.[14] OGD refers to this period as the filing review. The filing review takes approximately 60 days from the ANDA's receipt date to complete it.

If OGD determines that an ANDA is sufficiently complete, it simultaneously assigns the ANDA to Bioequivalence, Chemistry, and Labeling, as well as Microbiology (if required).[15] Each division begins its review when the ANDA reaches the top of the division's waiting list (i.e., queue). Regardless of the outcome of one division's review, the other divisions generally review the ANDA independently.

According to OGD officials, each division follows CDER's first-in, first-reviewed policy except when Chemistry determines that an ANDA contains no Chemistry deficiencies. In this case, divisions that have not finished reviewing the ANDA assign high priority to it and move it to the top of their queues.

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[11] CDER MaPP 5200.6. "Issuing and Tracking of Consults." Available online at http://www.fda.gov/Cder/mapp/5200-6.pdf. Accessed on January 11, 2007.

[12] CDER MaPP 5240.3. "Review Order of Original ANDAs, Amendments, and Supplements." Available online at http://www.fda.gov/Cder/mapp/5240-3R.pdf. Accesssed on December 5, 2007.

[13] Ibid. Expedited reviews are granted for products that respond to current and anticipated public health emergencies; are under special review programs, such as the President's Emergency Plan for AIDS Relief (PEPFAR); have been identified as nationwide shortages; and are first-generic drugs for which there are no blocking patents or exclusivities. First generics are drugs that have never been approved before as generics and are generic products new to the market.

[14] 21 CFR § 314.101(b).

[15] An OGD official indicated that if an ANDA is not sufficiently complete, OGD rejects it and sends a "refuse-to-file" letter to the applicant. OGD issued refuse-to-file letters for approximately 9 percent of ANDAs in fiscal year (FY) 2006.

In addition, Chemistry's review outcome determines OGD's response to the applicant. According to FDA, Chemistry results are the primary consideration during the ANDA review because Chemistry determines pharmaceutical equivalence, which is a key concept in assessing a generic's therapeutic equivalence to a brand name drug. Chemistry's influence on OGD's response to the applicant and the review process in other divisions is explained in greater detail below.[16]

The Office of Generic Drug's response and review process if Chemistry identifies deficiencies in the Abbreviated New Drug Application. If an ANDA does not meet Chemistry's review standards (i.e., Chemistry finds deficiencies in the ANDA), OGD disapproves the ANDA and sends a "not-approvable" letter to the applicant.[17] The not-approvable letter summarizes the Chemistry deficiencies. According to OGD officials, most original ANDAs contain Chemistry deficiencies and are disapproved.[18] [19]

Even though OGD has issued a not-approvable letter and has disapproved the ANDA based on Chemistry deficiencies, the other divisions continue processing it. If an ANDA does not meet other divisions' review standards (i.e., other divisions find deficiencies in the ANDA), they issue deficiency letters directly to the applicant summarizing the deficiencies.

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[16] FDA provides various overviews of the ANDA review process. For example, the "Generic Drug (ANDA) Review Process" is a flowchart available online at http://www.fda.gov/cder/handbook/anda.htm. Accesssed on January 3, 2008. OGD officials indicated that the current review process is not accurately reflected in many of these overviews. We provide here our understanding of the current review process based on our contact with OGD officials. Our description may be inconsistent with previous FDA overviews of the process.

[17] 21 U.S.C. § 505(j)(5)(A); 21 CFR § 314.120(a).

[18] Remarks by Scott Gottlieb, Deputy Commissioner for Medical and Scientific Affairs, FDA. Speech before the Annual Generic Drug Forum. April 7, 2006. Available online at http://www.fda.gov/oc/speeches/2006/genericdrug0407.html. Accesssed on October 9, 2007. According to these remarks, 98 percent of original ANDAs were disapproved in 2004 and 93 percent were disapproved in 2005.

[19] FDA also refers to original ANDAs as ANDAs reviewed during the first review cycle. Throughout this report, our use of the term "original ANDAs" is synonymous with ANDAs reviewed during the first review cycle. Most ANDAs contain Chemistry deficiencies and are disapproved during the first review cycle.

Applicants do not submit new ANDAs in response to not-approvable or deficiency letters. Instead, applicants submit amendments to the appropriate division(s) to correct ANDA deficiencies.[20]

OGD classifies amendments as major or minor.[21] Major amendments contain significant new data. Major amendments have the same review priority as original, unreviewed ANDAs and are reviewed according to CDER's first-in, first-reviewed policy.[22] In contrast, minor amendments do not contain significant new data and often indicate that an ANDA is close to approval. When OGD receives a minor amendment, it assigns high priority to it. The division places the minor amendment at the top of its queue, and the reviewer assigned to the ANDA reviews it upon completing his or her current assignment.

The Office of Generic Drugs response and review process if Chemistry does not identify deficiencies in the Abbreviated New Drug Application. If Chemistry does not find deficiencies in an ANDA, the other divisions must review it and resolve any deficiencies before OGD sends an approval letter. After each division determines that the ANDA contains no deficiencies, it notifies Chemistry that the ANDA is approvable within that division. Unlike not-approvable letters, OGD sends an approval letter only when all division reviews are complete and the ANDA contains no deficiencies.[23]

If other divisions find deficiencies in an ANDA but Chemistry does not, OGD does not disapprove the ANDA. However, the applicant must resolve the deficiencies before OGD will approve the ANDA. Therefore, when Chemistry does not identify deficiencies in an ANDA and is ready to approve it, the other divisions assign high priority to that ANDA.

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[20] 21 CFR § 314.96(a).

[21] CDER, Guidance for Industry. "Major, Minor, and Telephone Amendments to Abbreviated New Drug Applications." Available online at http://www.fda.gov/cder/guidance/4706fnl.pdf. Accesssed on December 13, 2006.

[22] Ibid.

[23] 21 CFR § 314.105(d).

According to CDER, 535 ANDAs (and corresponding amendments) were approved in 2006.[24] CDER indicates that median approval time for these ANDAs and amendments was nearly 17 months.[25]

Abbreviated New Drug Applications With Valid Patents or Exclusivities

In some cases, OGD can only "tentatively approve" an ANDA after all divisions have deemed the ANDA approvable.[26] For example, OGD can only tentatively approve an ANDA if valid patents or exclusive marketing rights (exclusivities) exist for brand name drugs.

The tentative-approval letter instructs the applicant to notify OGD of any updates to the ANDA within 90 days prior to the patent or exclusivity expiration date. OGD confirms that the ANDA is approvable by all divisions and sends an approval letter to the applicant once the patent or exclusivity expires.

Patents on brand name drugs are granted by the U.S. Patent and Trademark Office and are typically valid for 20 years from the date on which the patent was submitted.[27] Exclusivities are granted by FDA upon approval of a drug and may last up to 7 years.[28] Generally, OGD does not prioritize ANDA reviews according to the dates on which the patents or exclusivities expire (i.e., market entry date).

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[24] This includes ANDAs approved with delayed effective dates. "FDA 2006 Accomplishments: Thousands of Safe and Effective Health Care Products Made Available for Patients." Available online at http://www.fda.gov/oc/accomplishments/healthcare.html. Accesssed on May 5, 2008.

[25] Approval time is calculated from the time OGD receives the original ANDA to the time it is approved or tentatively approved. Approval time includes filing review time as well as the time necessary for applicants to prepare and submit, and for OGD to review and approve or tentatively approve, all amendments to the ANDA. Ted Sherwood, Office of Pharmaceutical Science in CDER at FDA. "Generic Drugs: Overview of ANDA Review Process." Available online at.http://www.fda.gov/cder/audiences/iact/forum/200704_sherwood.pdf. Accesssed on June 26, 2007.

[26] 21 CFR §§ 314.105(d) and 314.107. Although the term "approval letters with delayed effective dates" is cited in regulation, OGD officials referred to these letters as tentative-approval letters.

[27] U.S. Patent and Trademark Office. "General Information Concerning Patents: Nature of Patent and Patent Rights." Available online at http://www.uspto.gov/go/pac/doc/general/. Accesssed on July 27, 2007.

[28] FDA, CDER. "Frequently Asked Questions on Patents and Exclusivity." Available online at http://www.fda.gov/cder/ob/faqs.htm. Accesssed on November 8, 2007.

The Food and Drug Administration's 180-Day Review Requirement

The Federal Food, Drug, and Cosmetic Act requires FDA to approve or disapprove an ANDA within 180 days of initial receipt.[29] This 180-day period is called the "review clock."[30]

The 180-day review clock starts on the date on which OGD receives an ANDA (before the filing review) and stops on the date on which OGD sends an approval letter, a tentative-approval letter, or a not-approvable letter.[31] [32] If Chemistry identifies deficiencies in an original ANDA, OGD sends a not-approvable letter, and the 180-day review clock stops. If Chemistry identifies no deficiencies in the ANDA, OGD sends an approval or a tentative-approval letter once all remaining divisions deem the application approvable. According to OGD, Bioequivalence, Labeling, and Microbiology deficiency letters do not stop the 180-day review clock.

Proposed rule requires all divisions to meet the 180-day review clock. FDA issued a proposed rule in 2004 that would require OGD to send a "complete response" letter to the applicant within 180 days of receipt if an ANDA contains deficiencies.[33] The proposed rule specifies that a complete response letter will describe all of the deficiencies that the applicant must address before OGD can approve the ANDA.

According to current OGD practice, all divisions must meet the 180-day review clock if Chemistry finds no deficiencies in the original ANDA. However, if Chemistry finds deficiencies, only Chemistry is required to

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[29] Section 505(j)(5)(A) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. § 355(j)(5)(A)); 21 CFR § 314.100.

[30] 21 CFR § 314.100(a). The law would permit the applicant and FDA to extend this 180-day period by mutual agreement. However, OGD officials indicated that they do not extend the review clock.

[31] Ibid. If OGD deems an ANDA to be sufficiently complete under 21 CFR § 314.101(b), the 180-day review clock starts retroactively on the date of receipt. If OGD deems an ANDA not to be sufficiently complete, the 180-day review clock does not start. If OGD deems a revised and resubmitted ANDA to be sufficiently complete, the 180-day review clock retroactively starts on the date of the resubmission.

[32] Pursuant to 21 CFR § 314.100(a), FDA may also send an approvable letter under 21 CFR § 314.110 to stop the 180-day review clock. However, OGD officials stated that they no longer send approvable letters. We confirmed this practice in OGD's monthly statistics report, which provides data on OGD actions for original ANDAs in the past 5 years. According to this internal report, OGD has not sent an approvable letter since April 2004. Therefore, we did not include these letters in our review.

[33] Applications for Approval To Market a New Drug; Complete Response Letter; Amendments to Unapproved Applications, 69 Fed. Reg. 43352, 43355–43356 (proposed July 20, 2004).

meet the 180-day review clock. Therefore, when OGD sends a not-approvable letter based on Chemistry deficiencies, the 180-day review clock stops.

In contrast, to comply with the proposed rule, all divisions will need to meet the 180-day review clock regardless of whether Chemistry finds deficiencies in the ANDA.[34]

Review Resources at the Food and Drug Administration

The number of ANDAs submitted to OGD has increased at more than double the rate of growth of OGD's review resources for ANDAs in the last 5 years. Despite this disproportionate growth, OGD's approval times have decreased.[35]

Funding for the Generic Drugs Program has increased by 74 percent in the last 5 years, from $35.9 million in FY 2001 to $62.6 million in FY 2006.[36] [37] The number of full-time-equivalent positions in OGD increased by 50 percent during this same time period, from 134 in FY 2001 to 201 in FY 2006.[38]

In contrast, according to CDER, the number of original ANDAs submitted between FYs 2001 and 2006 increased by 158 percent, from 307 to 793.[39] [40]

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[34] According to a recent Semiannual Regulatory Agenda published in the Federal Register, the Department of Health and Human Services estimated that it would publish the final rule in October 2007 (72 Fed. Reg. 22490 (Apr. 30, 2007)). Available online at http://frwebgate.access.gpo.gov/ cgi-bin/getdoc.cgi?dbname=2007_unified_agenda_&docid=f:ua070408.wais. Accesssed on August 29, 2007. As of January 16, 2008, FDA had not published the final rule.

[35] Ted Sherwood, Office of Pharmaceutical Science in CDER at FDA. "Generic Drugs: Overview of ANDA Review Process." Available online at http://www.fda.gov/cder/audiences/iact/forum/200704_sherwood.pdf. Accesssed on June 26, 2007.

[36] The Generic Drugs Program includes OGD and other FDA offices associated with the generic drug review process, such as the Office of Regulatory Affairs and CDER's Office of Compliance, Office of Regulatory Policy, and Office of New Drugs.

[37] Generic Drugs Program budget figures were obtained from FDA officials in June 2007.

[38] Gary Buehler, OGD Director. "Improving Access to Generic Drugs." Testimony before the United States Senate Special Committee on Aging. July 20, 2006. Available online at http://aging.senate.gov/events/hr161gb.pdf. Accesssed on July 25, 2007.

[39] Ted Sherwood, Office of Pharmaceutical Science in CDER at FDA. "Generic Drugs: Overview of ANDA Review Process." Available online at http://www.fda.gov/cder/audiences/iact/forum/200704_sherwood.pdf. Accesssed on June 26, 2007.

[40] These 793 ANDAs were submitted to OGD in FY 2006. The number of ANDAs in our analysis—989—is greater than 793 because we included ANDAs that were submitted or were under review in calendar year 2006. Our analysis also includes ANDAs submitted before 2006.

FDA continues to revise the ANDA review process to improve approval times and has made progress since 2001.[41] According to CDER, median approval time for ANDAs decreased nearly 2 months from 2001 to 2006.[42]

Currently, congressional appropriations fund ANDA reviews. To supplement FDA's budget, the President's proposed budget for FY 2009 includes over $16 million for ANDA reviews funded through a new user fee program.[43] User fees would support CDER's review by requiring applicants to pay fees when submitting original ANDAs.

Related Office of Inspector General Work

In 2003, the Office of Inspector General (OIG) reviewed the CDER Office of New Drugs' management of the new drug application review process for brand name drugs.[44] OIG found that there were general workload concerns but that the review process had several strengths. OIG recommended ways for FDA to manage review resources, including assessing workload pressures and rejecting poor-quality applications.

In 1989, OIG reviewed FDA's generic drug approval process.[45] OIG concluded that the process for assigning ANDAs to reviewers was arbitrary and could permit favoritism to certain applicants. OIG recommended that FDA consistently apply its first-in, first-reviewed policy for reviewing ANDAs. OIG also recommended that FDA uniformly apply and properly document exceptions to this policy.

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[41] For example, "FDA Announces Initiative To Bolster Generic Drug Program." October 4, 2007. Available online at http://www.fda.gov/bbs/topics/NEWS/2007/NEW01719.html. Accesssed on November 2, 2007. This particular initiative was incorporated into CDER's MaPP 5240.3 and became effective October 18, 2006.

[42] Ted Sherwood, Office of Pharmaceutical Science in CDER at FDA. "Generic Drugs: Overview of ANDA Review Process." Available online at http://www.fda.gov/cder/audiences/iact/forum/200704_sherwood.pdf. Accesssed on June 26, 2007.

[43] FDA. "Summary of FDA's FY 2009 Budget." Available online at http://www.fda.gov/oc/factsheets/budget2009.html. Accesssed on February 28, 2008.

[44] "FDA's Review Process for New Drug Applications: A Management Review," OEI-01-01-00590.

[45] "Vulnerabilities in the Food and Drug Administration's Generic Drug Approval Process," A-15-89-00051.

METHODOLOGY

Scope

We examined review times for 989 original ANDAs that were approved, tentatively approved, disapproved, or pending (i.e., the ANDAs had not been reviewed or the reviews were not complete) during 2006.[46] [47] See Appendix A for additional information about our methodology, including criteria for excluding ANDAs from our analyses.

We surveyed OGD division reviewers and conducted structured interviews with OGD officials to determine factors that affect ANDA review times.

Data Sources

We obtained information about FDA's generic drug review process from the following sources:

- FDA statutes, regulations, policies, procedures, and guidance documents;
- FDA's Centerwide Oracle Management Information System (COMIS);
- Surveys of OGD reviewers assigned to a sample of original ANDAs under review in 2006 with review times greater than 180 days;
- Structured interviews with OGD officials involved in the generic drug review process; and
- OGD's consult database.

Data Collection and Analysis

We reviewed FDA law, policies, procedures, and guidance documents to understand the generic drug review process. We compared these documents with information obtained from OGD officials regarding OGD practices. In addition, we analyzed data obtained from COMIS to verify OGD practices.

We analyzed 989 original ANDAs to determine review times in each division. Of the 989 original ANDAs, we identified those with review

[46] This includes ANDAs that were submitted in 2005 and were under review in 2006 or were submitted in 2006 but were reviewed or pending longer than 180 days in 2007.

[47] The term "original" refers to new, sufficiently complete ANDAs. It does not include amendments.

times greater than 180 days in each division and selected a sample of 105 ANDAs.

We surveyed OGD reviewers responsible for reviewing the sample of 105 ANDAs. We surveyed reviewers about factors contributing to original ANDA review times exceeding 180 days.

We conducted structured interviews with 12 OGD officials involved in the administration of the generic drug review process to identify factors contributing to longer review times throughout the review process, from ANDA receipt to approval.

Finally, we examined the OGD consult database to determine the number of and review times for pending consults.

Limitations

We did not independently verify the COMIS data or the OGD consult data to ensure their accuracy.

Almost all original ANDAs are disapproved because Chemistry finds deficiencies. Therefore, we determined the extent to which original ANDA review times exceeded the 180-day review clock by analyzing Chemistry review times. We did not determine the extent to which original ANDA review times exceeded the 180-day review clock in other divisions when Chemistry did not find deficiencies.

The results from our sample of 105 ANDAs with review times greater than 180 days are not projectable.

Shorter ANDA review times cannot be directly linked to faster market entry because of valid patents or exclusivities or applicants' marketing decisions. For example, an ANDA can be approvable by all divisions within 180 days, but valid patents or exclusivities prevent OGD from approving the ANDA. OGD can only tentatively approve ANDAs before valid patents or exclusivities expire. Once OGD approves ANDAs, applicants' marketing decisions may further delay or prevent drugs' market entry.

Standards

We conducted this review 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.

The Food and Drug Administration approved or tentatively approved 4 percent of original Abbreviated New Drug Applications under review in 2006; the remaining 96 percent did not meet review standards and were disapproved

FDA's OGD approved 1 percent and tentatively approved 3 percent of original ANDAs under review in 2006.[48] [49] OGD approves or tentatively approves ANDAs that meet each division's review standards.[50] If an ANDA does not meet all review standards (i.e., the ANDA contains deficiencies in at least one division), OGD cannot approve it.

Generally, approval status (i.e., approved, tentatively approved, or disapproved) is based on whether (1) Chemistry identifies deficiencies in the ANDA and (2) valid patents or exclusivities exist for the brand name drug.

OGD approved 1 percent of original ANDAs (9 of 989) under review in 2006. No OGD divisions found deficiencies in these ANDAs, and valid patents or exclusivities did not exist for the brand name drugs.[51] Applicants could market these generic drugs as soon as OGD approved the ANDAs.

OGD tentatively approved 3 percent of original ANDAs (34 of 989) under review in 2006. No divisions found deficiencies in these ANDAs, but valid patents or exclusivities existed for the brand name drugs.[52] Applicants cannot market generic drugs until patents or exclusivities expire or are deemed invalid through litigation.

OGD disapproved 96 percent of original ANDAs (946 of 989) under review in 2006. OGD disapproves ANDAs and sends not-approvable letters to applicants when ANDAs do not meet Chemistry's review standards.

To correct the deficiencies noted in not-approvable or deficiency letters, applicants submit major or minor amendments. OGD receives a large

[48] FDA approved a total of 535 ANDAs in 2006. This included approved or tentatively approved original ANDAs and those requiring amendments. In contrast, our review included only original ANDAs.

[49] These original ANDAs were approved or tentatively approved during the first review cycle.

[50] 21 CFR § 314.105(d).

[51] If Bioequivalence, Labeling, or Microbiology found deficiencies in these ANDAs, the deficiencies were resolved before OGD approved the ANDAs.

[52] If Bioequivalence, Labeling, or Microbiology found deficiencies in these ANDAs, the deficiencies were resolved before OGD tentatively approved the ANDAs.

number of amendments because most ANDAs do not meet OGD's review standards and are initially disapproved. For example, OGD received 828 original ANDAs under review in 2006 but received 4,174 major or minor Chemistry amendments.[53]

Major and minor amendments compete for the same review resources as original ANDAs. Upon receipt, major amendments are placed at the end of the same queue as original ANDAs. Minor amendments are placed ahead of original ANDAs and major amendments in the queue.

The Food and Drug Administration exceeded the 180-day review requirement for nearly half of original Abbreviated New Drug Applications under review in 2006 because Chemistry reviews exceeded 180 days

Forty-six percent of original ANDA Chemistry reviews (456 of 989) exceeded the 180-day requirement in 2006.[54] For these ANDAs, the median review time was 217 days. Chemistry review time ranges are presented in Appendix B.

Table 1 (on the next page) provides the number of original ANDAs under review by FDA's OGD in 2006 as well as the number, percentage, and median review time for ANDAs having review times greater than 180 days. Table 1 presents these data by ANDA approval status. Because Chemistry found deficiencies in most original ANDAs under review in 2006 and stopped the 180-day review clock, Table 1 contains data for Chemistry only.[55]

[53] These 828 ANDAs were submitted to OGD in 2006. The number of ANDAs in our analysis—989—is greater than 828 because we included ANDAs that were submitted or were under review in 2006. Thus, our analysis includes ANDAs submitted before 2006.

[54] Our analysis of the number of original ANDAs exceeding the 180-day review clock is conservative. Because of limitations in the COMIS database, we calculated compliance with the 180-day review clock based on Chemistry review time (from the date on which OGD received the ANDA to the date on which Chemistry completed its review) rather than OGD response time (from the date on which OGD received the ANDA to the date on which OGD sent an approval letter, a tentative-approval letter, or a not-approvable letter). For example, if Chemistry completed its review on Day 185 and found no deficiencies and OGD sent an approval letter on Day 210 (once other divisions deemed the ANDA approvable), our calculation of Chemistry review time would be 185 days. In contrast, pursuant to 21 CFR § 314.100, the 180-day review clock would not stop until Day 210.

[55] One ANDA was pending longer than 180 days at the time we collected the data. FDA later indicated that this ANDA was disapproved and provided the date on which Chemistry completed its review. We used this date to calculate review time for this ANDA, which was included in our analysis of Chemistry's ANDA review times.

Table 1: 2006 Chemistry Reviews of Original Abbreviated New Drug Applications

ANDA Approval Status	Number of ANDAs Reviewed	Number of ANDAs With Review Time > 180 Days	Percentage of ANDAs With Review Time > 180 Days	Median Review Time for ANDAs With Review Time > 180 Days
Approved	9	5	56%	268 days
Tentatively Approved	34	23	68%	300 days
Disapproved	946	428	45%	214 days
All	**989**	**456**	**46%**	**217 days**

Source: OIG analysis of FDA COMIS data, 2007.

The percentage of ANDAs with review times longer than 180 days, and median review times for these ANDAs, varied according to ANDA approval status:

- *Approved Abbreviated New Drug Applications.* Five of the nine original ANDAs approved in 2006 were not reviewed within 180 days. For these five ANDAs, applicants waited a median of 268 days (i.e., almost 3 months beyond the 180-day regulatory timeframe) before they received OGD's approval and could market the drugs.
- *Tentatively Approved Abbreviated New Drug Applications.* Reviews for 23 of the 34 tentatively approved original ANDAs exceeded 180 days. Applicants waited a median of 300 days (i.e., 4 months beyond the 180-day regulatory timeframe) for OGD to tentatively approve these ANDAs.

  Regardless of whether OGD reviewed these tentatively approved ANDAs within 180 days, applicants could not market these drugs immediately because of valid patents or exclusivities. For example, even though OGD tentatively approved 11 of the 34 ANDAs within 180 days, the patent expiration dates for the brand name drugs ranged from 11 months to 12 years after the date of OGD's tentative approval.[56] [57] [58]

[56] The earliest expiration date was November 22, 2007, but OGD tentatively approved this ANDA on December 29, 2006 (i.e., 11 months before the patent expired). The latest expiration date was November 14, 2018, and OGD tentatively approved this ANDA on November 6, 2006 (i.e., 12 years before the patent expired).

[57] Applicants for 2 of the 11 ANDAs were challenging the validity of the patents or exclusivities.

[58] Five of these ANDAs were expedited PEPFAR applications. Although patents prevent marketing these drugs in the United States, applicants can market them internationally.

- *Disapproved Abbreviated New Drug Applications.* Reviews for 428 disapproved original ANDAs exceeded 180 days. For these ANDAs, applicants waited a median of 214 days (i.e., more than 1 month beyond the expiration of the 180-day review clock) before OGD notified them of the ANDA disapproval.

Microbiology, Bioequivalence, and Labeling reviews of original Abbreviated New Drug Applications generally exceeded 180 days in 2006

In 2006, 77 percent of original ANDAs (760 of 989) had review times exceeding 180 days in divisions other than Chemistry. Of ANDAs taking more than 180 days to review, median review times were 361 days in Microbiology, 287 days in Bioequivalence, and 277 days in Labeling. Review time ranges in each division are presented in Appendix C.

OGD does not hold these other divisions (i.e., Microbiology, Bioequivalence, and Labeling) to the 180-day review clock if Chemistry finds deficiencies in the original ANDA. However, FDA's proposed rule will require all divisions to complete reviews within 180 days, regardless of whether Chemistry finds deficiencies.[59]

Table 2 (on the next page) provides, by division, the number of original ANDAs under review in Microbiology, Bioequivalence, and Labeling in 2006 as well as the number, percentage, and median review times for ANDAs having review times greater than 180 days.[60]

[59] Applications for Approval To Market a New Drug; Complete Response Letter; Amendments to Unapproved Applications, 69 Fed. Red. (proposed July 20, 2004).

[60] Data are not available in COMIS to determine the review outcome (i.e., approvable or deficient) in divisions other than Chemistry.

Table 2: 2006 Microbiology, Bioequivalence, and Labeling Reviews of Original Abbreviated New Drug Applications

OGD Division	Total Number of ANDAs Reviewed	Number of ANDAs With Review Time > 180 Days	Percentage of ANDAs With Review Time > 180 Days*	Median Review Time for ANDAs With Review Time > 180 Days**
Microbiology	229	175	76%	361 days
Bioequivalence	989	576	58%	287 days
Labeling	989	556	56%	277 days

* Some ANDAs had reviews that exceeded 180 days in multiple divisions.

** Median review times may be underestimated because review times for pending ANDAs in these divisions were accruing when we obtained the data. Of ANDAs with review times greater than 180 days, the percentages that were pending at the time we obtained the data were: 73 percent for Microbiology (127 of 175 ANDAs), 3 percent for Bioequivalence (16 of 576 ANDAs), and 32 percent for Labeling (178 of 556 ANDAs).

Source: OIG analysis of FDA COMIS data, 2007.

Nearly 70 percent of sampled division reviews exceeding 180 days did not begin before the 180-day review periods expired

In our sample of ANDAs with review times exceeding 180 days, 69 percent (72 of 105) of original ANDAs were in the queue longer than 180 days.[61] Thus, the 180-day periods passed before division reviews began in most of our sample of 105 original ANDAs.

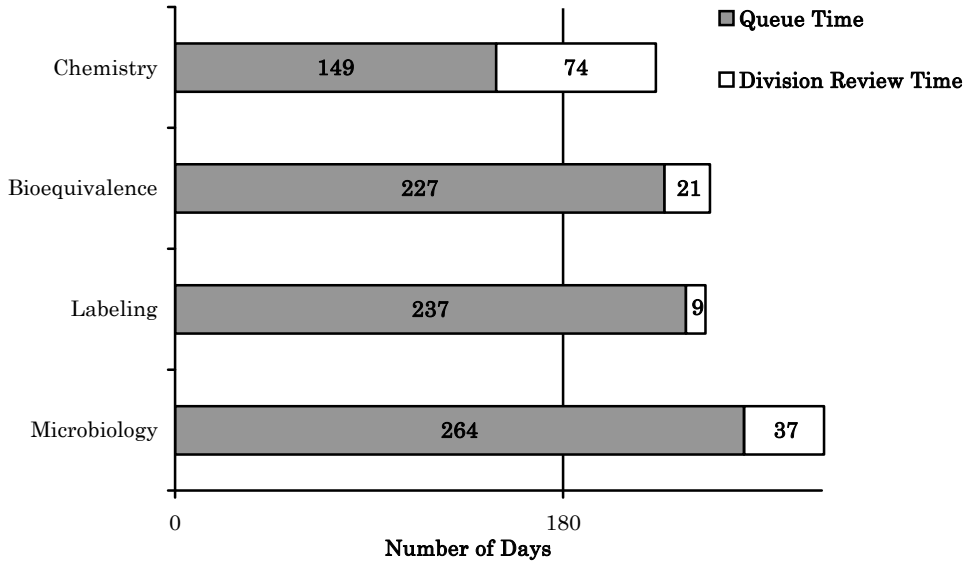
Review time in each division is calculated from the date on which OGD receives an ANDA to the date on which each division completes its review of the original ANDA. Review times can be further divided into two components: the amount of time the ANDA waited in the queue (i.e., queue time) and the amount of time each division took to determine whether the ANDA met the division's review standards (i.e., division review time).[62]

Figure 1 (on the next page) compares medians for queue time and division review time for the sample of 105 ANDAs having review times greater than 180 days in each division.

[61] These data are available for the sample of 105 ANDAs only. The dates on which reviewers start their reviews (i.e., the dates on which ANDAs leave the queue) are not provided in the COMIS; reviewers in our sample provided these dates in their survey responses.

[62] Queue time consists of both the filing review time and the time the ANDA awaits review in the division queue.

FIGURE 1
Comparison Between Queue Time and Division Review Time by Division



Source: OIG analysis of FDA COMIS data and OGD reviewer responses, 2007.

The Food and Drug Administration's prioritization practices affect Abbreviated New Drug Application review times

FDA prioritization practices contribute to longer review times for ANDAs close to approval. ANDAs that are close to approval include those that (1) have high-priority consults; (2) do not have valid patents or exclusivities, or have patents or exclusivities that will expire in the near future; (3) are deemed approvable in multiple divisions; or (4) contain only minor deficiencies.

The Food and Drug Administration does not review consults within policy timeframes

FDA's CDER policy indicates that OGD should receive consult results for highest-priority consults within 15 days and lowest-priority consults within 90 days. Consult priority is based, in part, on how close the ANDA is to approval. In practice, however, consult results generally are not returned to OGD within the timeframes specified in policy, which prolongs ANDA review times.

For the 100 pending OGD consults, days pending ranged from 3 to 882.[63] Of these pending consults, 78 percent (78 of 100) were not

[63] These consults were pending as of June 22, 2007, the date on which we received the OGD consult data.

returned to OGD within 90 days (i.e., the longest period of time specified by CDER policy). Sixty-eight percent (68 of 100) were not returned within 180 days. The number of days pending for all 100 consults is presented in Appendix D.

The Food and Drug Administration does not consider market entry date when prioritizing Abbreviated New Drug Applications

FDA's OGD generally maintains a first-in, first-reviewed policy for reviewing ANDAs. FDA grants exceptions to this policy, such as for first generic drugs that do not have valid patents or exclusivities at the time of submission.[64]

However, FDA does not grant exceptions to this policy for ANDAs of non-first generic drugs without patents or exclusivities (i.e., ANDAs that are close to approval rather than tentative approval).[65] Thus, OGD reviews ANDAs with valid patents or exclusivities while ANDAs that can immediately enter the market wait in the queue.

Twenty-nine percent (291 of 989) of original ANDAs under review by OGD in 2006 could not immediately enter the market because of valid patents or exclusivities. Chemistry reviewed nearly 60 percent of these ANDAs (168 of 291) within 180 days.

In contrast, 71 percent (698 of 989) of original ANDAs under review in 2006 could enter the market as soon as OGD approved them.[66] Chemistry reviewed only 52 percent of these ANDAs (365 of 698) within 180 days.

The Food and Drug Administration prioritizes Abbreviated New Drug Applications differently across divisions

FDA's OGD prioritizes ANDAs with approvable reviews differently across divisions. Divisions also classify and prioritize amendments differently. Differences in prioritizing ANDAs affect ANDA review times, as described below.

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[64] First generics are drugs that have never been approved before as generics and are new to the market.

[65] According to FDA, the second and subsequent generic drugs to enter the market effect the greatest cost savings. First generic drugs are priced only slightly lower than brand name drugs. Available online at http://www.fda.gov/cder/ogd/generic_competition.htm. Accesssed on February 18, 2008.

[66] This includes ANDAs in which the applicants are challenging the validity of the patents or exclusivities.

Divisions in the Office of Generic Drugs do not consistently assign high priority to approvable Abbreviated New Drug Applications. Other OGD divisions assign high priority to an ANDA after Chemistry deems the ANDA approvable. However, Chemistry maintains CDER's first-in, first-reviewed policy and does not change the priority of ANDAs deemed approvable by other divisions.

For example, if Chemistry deems an ANDA approvable before other divisions, the ANDA is designated as high priority and reviewed ahead of other ANDAs in divisions' queues.[67] In contrast, if all three non-Chemistry divisions deem an ANDA approvable, Chemistry does not assign high priority to the ANDA. Rather, Chemistry reviews the ANDA according to CDER's first-in, first-reviewed policy.

Divisions in the Office of Generic Drugs do not consistently classify and prioritize amendments. Federal regulation recognizes that amendments that contain significant new data will require significant additional review time.[68] Pursuant to CDER guidance, these major amendments have the same review priority as original, unreviewed ANDAs.[69] CDER guidance also directs OGD to classify all other amendments as minor. When minor amendments are received, divisions should assign high priority to them to expedite the review of ANDAs that are near approval.[70]

According to FDA, only Chemistry classifies amendments as major or minor.[71] [72] In addition, during our structured interviews, an OGD official stated that amendments in non-Chemistry divisions are treated as minor amendments and prioritized ahead of original

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[67] The other divisions also assign high priority to any amendments they receive for the ANDA.

[68] 21 CFR § 314.96(a).

[69] CDER, Guidance for Industry. "Major, Minor, and Telephone Amendments to Abbreviated New Drug Applications." Available online at http://www.fda.gov/cder/guidance/4706fnl.pdf. Accesssed on December 13, 2006.

[70] Ibid.

[71] For example, see Ted Sherwood, Office of Pharmaceutical Science in CDER at FDA. "Generic Drugs: Overview of ANDA Review Process." Available online at http://www.fda.gov/cder/audiences/iact/forum/200704_sherwood.pdf. Accesssed on June 26, 2007.

[72] We confirmed this OGD practice by examining COMIS data. A COMIS data field tracks major and minor amendments for Chemistry. Codes in other divisions do not designate amendments as major or minor.

ANDAs in the queue, regardless of the significance of the data contained in the amendment.

Not classifying amendments as major or minor may place ANDAs with more deficiencies ahead of those with fewer. This may dilute the effectiveness of the amendment prioritization process by delaying reviews of amendments that are truly minor and original ANDAs.

Generic drugs are generally thought of as one way to rein in increasing health costs. FDA's timeliness in approving generic drugs has recently been a topic of scrutiny by both Congress and the media. Federal law requires that FDA approve or disapprove original ANDAs within 180 days of receipt.

We found that FDA disapproved most original ANDAs under review in 2006 because they did not meet FDA review standards. Nearly half of Chemistry review times exceeded the 180 days required by Federal law. Moreover, many review times in other OGD divisions exceeded 180 days. In addition, for a sample of ANDA reviews exceeding 180 days, most reviews did not begin before the 180-day periods expired. Finally, we found that FDA prioritization practices affect ANDA review times.

The ANDA submissions have increased at more than double the rate of review resources in the last 5 years. To better manage OGD's current ANDA reviews and to potentially increase the number of ANDAs reviewed and approved within 180 days, we recommend that FDA:

Identify Common Original Abbreviated New Drug Application Deficiencies and Offer More Guidance to Industry To Decrease the Percentage Disapproved

Without lowering review standards, FDA should identify ways to decrease the percentage of disapproved original ANDAs. Disapproving fewer original ANDAs would reduce the number of amendments that FDA's OGD receives and reviews. If OGD received fewer amendments, the queue would become smaller, and OGD could allocate more resources to review original ANDAs within 180 days.

To decrease the percentage of ANDAs originally disapproved, we suggest that OGD examine deficiency letters to identify common deficiencies in original ANDAs. The types of deficiencies that occur most frequently indicate the areas in which applicants need more guidance. FDA should create or revise guidance to address these problem areas. Expanded guidance may improve the quality of the ANDAs submitted to OGD and increase the percentage of original ANDAs approved within 180 days.

Increase the Percentage of Original Abbreviated New Drug Applications Reviewed by All Divisions Within 180 Days

Federal regulation requires that FDA approve or disapprove original ANDAs within 180 days of receipt. In addition, FDA's proposed rule would require that all divisions review ANDAs within the 180-day regulatory requirement, regardless of whether Chemistry identifies deficiencies in the original ANDAs.

In light of the current regulation and proposed rule, FDA should continue to revise the ANDA review process to reduce review times in all divisions. Because queue times in our sample of ANDAs were longer than division review times and the 180-day period passed while most of our sample waited in the queue, FDA should focus on reducing queue times.

Identify New Prioritization Practices To Reduce Review Times for Abbreviated New Drug Applications Close to Approval

ANDAs that are close to approval include those that have high-priority consults, have no valid patents or exclusivities (or have patents or exclusivities that expire soon), are deemed approvable in multiple divisions, or contain only minor deficiencies.

We recommend that FDA assign priority to and meet review timeframes for consults based on whether the ANDAs are close to approval, according to CDER's consult policy. In addition, FDA should identify ANDAs close to approval and improve the prioritization process to reduce review times for these ANDAs. These new prioritization processes would generate exceptions to CDER's first-in, first-reviewed policy for reviewing ANDAs. If implemented, OGD would need to uniformly apply and properly document these exceptions.

Evaluate the consultation process to meet review timeframes specified by Food and Drug Administration policy. FDA's CDER policy defines high- and low-priority consults based, in part, on whether the ANDA is close to approval. The policy also establishes review timeframes based on the consult's priority. However, we found that, in practice, consult results generally are not returned to OGD within specified timeframes, regardless of the consult's priority.

FDA should examine the ANDA consultation process to determine how consults can be returned to OGD within the timeframes specified in CDER policy, particularly consults for ANDAs close to approval. Obtaining consults within designated priority timeframes may reduce the number of ANDAs exceeding the 180-day regulatory requirement.

Identify and assign high priority to Abbreviated New Drug Applications close to approval. Assigning high priority to some ANDAs will reduce review times for these ANDAs but will also delay reviews for lower-priority ANDAs. In light of this, we offer the following options to FDA's OGD for identifying ANDAs that are close to approval and improving the ANDA prioritization process. We also recognize that there may be additional options to improve the prioritization process.

- *Prioritize Abbreviated New Drug Applications based on potential market entry date.* OGD could review ANDAs for generic drugs without valid patents or exclusivities ahead of those with them. OGD could assign high priority to and reduce review times for ANDAs that can be approved and marketed immediately (i.e., ANDAs without valid patents or exclusivities) or in the near future (i.e., ANDAs with valid patents or exclusivities expiring soon). However, OGD should not delay ANDA reviews if the delay violates current FDA policy (e.g., ANDAs expedited under the PEPFAR program or expedited first generic drugs).
- *Assign high priority to Abbreviated New Drug Applications with approvable reviews in multiple divisions.* OGD could prioritize ANDAs based on the number of divisions with approvable reviews. As a result, ANDAs with few deficiencies across divisions (i.e., ANDAs approvable by multiple divisions and, thus, close to approval) would be reviewed more quickly.
- *Classify amendments according to Food and Drug Administration policy and assign high priority to Abbreviated New Drug Applications with only minor deficiencies.* OGD could follow or revise amendment policies so that divisions classify and prioritize amendments similarly. In all divisions, OGD could assign high priority to ANDAs with minor deficiencies (i.e., ANDAs close to approval) and review them before ANDAs with major deficiencies.

AGENCY COMMENTS

In its comments to the draft report, FDA noted that OGD and CDER staff have already identified portions of the primary recommendations, and FDA is implementing process improvements that are the same as or similar to the recommendations. Specifically, FDA agreed with our first recommendation but did not indicate whether it concurred with the two additional recommendations.

FDA agreed that increasing the number of original ANDAs approved (i.e., in the first review cycle) would help streamline the review process by decreasing the number of amendments and subsequent review cycles. FDA has provided guidance to assist industry in submitting more easily reviewed applications and indicated that the development of guidance is a continually evolving process.

Although FDA did not indicate whether it concurred with the second recommendation, FDA noted that it continues to alter its review process with the goals of reducing queue times and reviewing original ANDAs within 180 days. FDA has developed a focused hiring program to increase staff and anticipates that additional reviewers will eventually decrease review times. In addition, FDA is developing other approaches to increase review efficiency, including shifting responsibilities to the Project Management staff.

FDA also did not indicate whether it concurred with the last recommendation. FDA stated that a variety of external forces can affect an application's review and approval, which makes determining whether an ANDA is "close to approval" difficult. FDA also expressed some concerns about the options presented in our recommendation. However, it appears that FDA has taken some actions to address this recommendation. FDA noted that it prioritizes some ANDAs based on potential market entry date and may consider further revisions to this process. In particular, FDA indicated that a possible consideration would be to delay reviews for ANDAs with patents that expire far into the future. However, FDA noted that such a process would require a thorough examination of all related issues and policy changes within OGD.

FDA also provided several technical comments to the report. We have incorporated these comments into the report, as appropriate.

We ask that, in its final management decision, FDA more clearly indicate whether it concurs with each of our recommendations. For the full text of FDA's comments, see Appendix E.

ADDITIONAL INFORMATION ON METHODOLOGY

Below we provide additional information about the methodology used to accomplish our objectives.

Food and Drug Administration Policies, Procedures, and Guidance

We reviewed the Food and Drug Administration's (FDA) Center for Drug Evaluation and Research (CDER) policies, procedures, and guidance on the:

- issuance and tracking of consults in the Office of Generic Drugs (OGD),
- review order of original Abbreviated New Drug Applications (ANDAs) and amendments, and
- classification of major and minor amendments.

We compared these documents to information gathered about ANDA review practices from OGD officials as well as data obtained from FDA's Centerwide Oracle Management Information System (COMIS), surveys of OGD reviewers, and structured interviews with OGD officials. We identified generic drug review practices that deviated from CDER policies, procedures, or guidance. We also identified policies and practices that affected ANDA review times (e.g., OGD does not prioritize ANDAs based on potential market entry date).

Centerwide Oracle Management Information System Data

We obtained COMIS data from FDA to assess each division's review times for ANDAs under review in 2006. We defined ANDAs as "under review" if they contained a date between January 1 and December 31, 2006, in any of the following COMIS fields:

- the date on which the ANDA was addressed to OGD,
- the date on which at least one division completed its review of the ANDA, or
- the date on which Chemistry acted on the ANDA.

We obtained COMIS data for all ANDAs meeting at least one of the above criteria. Although we received data from FDA for 1,619 original ANDAs, we analyzed review times for 989 original ANDAs.

We removed data for 37 ANDAs because they did not meet our criteria of being submitted, in the review queue, under review, or reviewed by at

least one division in 2006. Additional records were removed from the data set if at least one of the following criteria was met:

- The ANDA was closed administratively or not assigned to divisions based on the results of the filing review (116 ANDAs),
- COMIS did not contain data for the ANDA in all three divisions that review each ANDA (Bioequivalence, Chemistry, and Labeling; 393 ANDAs), and
- The ANDA had been pending fewer than 180 days and Chemistry had not completed its review (84 ANDAs).

The COMIS data were analyzed using SAS,® a statistical analysis program. ANDA review times were calculated for each of the four divisions by subtracting the date on which OGD received the ANDA from the date on which each division completed its review. If an ANDA was currently pending in a division for more than 180 days, we entered the date on which we obtained the COMIS data from FDA (April 2, 2007) as the review completion date and assigned a pending code to the record.

In some cases, an ANDA contained multiple records for a division (e.g., Bioequivalence has multiple COMIS division codes that all reflect the Bioequivalence review). To capture the total time for a division to complete the ANDA review, the last date on which a review was completed in the division was used as the review stop date.

For cases in which one record for an ANDA within a division contained a review stop date but another record within the same division and ANDA contained no stop date, the last stop date was used. A review stop date indicates that the review is complete, and we did not classify these cases as pending.

Office of Generic Drugs Reviewers

From the COMIS data, we identified ANDAs with review times greater than 180 days and selected a sample of 105 ANDA reviews. To obtain this sample, we identified reviewers assigned to a subset of recently submitted ANDAs within each division. We sampled from ANDAs in which the 180-day review clock would have expired in the 4 months prior to the date on which we requested the data from FDA. These ANDAs were submitted from June through September 2006.

We randomly selected 25 tentatively approved, disapproved, or pending ANDAs within each division. In each division, we randomly selected one ANDA review per reviewer until each reviewer was sampled once or until 25 ANDA reviews were selected. If we did not obtain 25 ANDA reviews within a division after each reviewer was sampled once, we randomly selected additional ANDA reviews in the division, 1 per reviewer, until we obtained 25 ANDAs within the division.

We also selected all ANDAs that were approved but had review times greater than 180 days. This added five ANDA reviews to Chemistry and one ANDA review to Labeling for our sample.

Therefore, we collected data from reviewers for a total of 106 ANDA reviews: 30 Chemistry, 25 Bioequivalence, 26 Labeling, and 25 Microbiology. However, one Labeling reviewer indicated that the COMIS data for his review were wrong and the ANDA was reviewed within 180 days. We removed this ANDA review from our sample. Thus, our analysis of reviewer data was based on 105 ANDA reviews.

Reviewers' survey responses indicated the date on which their review of each ANDA began as well as the factors that contributed to the ANDA reviews' exceeding 180 days within their division.

Office of Generic Drugs Officials

We conducted structured interviews with a division director (in all divisions except Microbiology), team leader, and project manager from each of the divisions as well as the Director of OGD. We asked these 12 individuals open-ended questions concerning factors that contribute to longer review times throughout the generic drug review process.

We used reviewers' and officials' responses to understand ANDA review practices and to identify factors that contribute to ANDA review times exceeding 180 days. In addition, data from reviewers and officials provided the basis for collecting and analyzing additional FDA data. For example, reviewers' and officials' responses prompted us to examine the OGD consult data and to compare review times for ANDAs affected by valid patents or exclusivities with those that could enter the market immediately.

APPENDIX ~ B

2006 Chemistry Review Time Ranges

ANDA Approval Status	Review Time Range for ANDAs With Review Time > 180 Days
Approved	246–306 days
Tentatively Approved	187–667 days
Disapproved	181–816 days
All	**181–816 days**

Source: Office of Inspector General analysis of FDA COMIS data, 2007.

APPENDIX ~ C

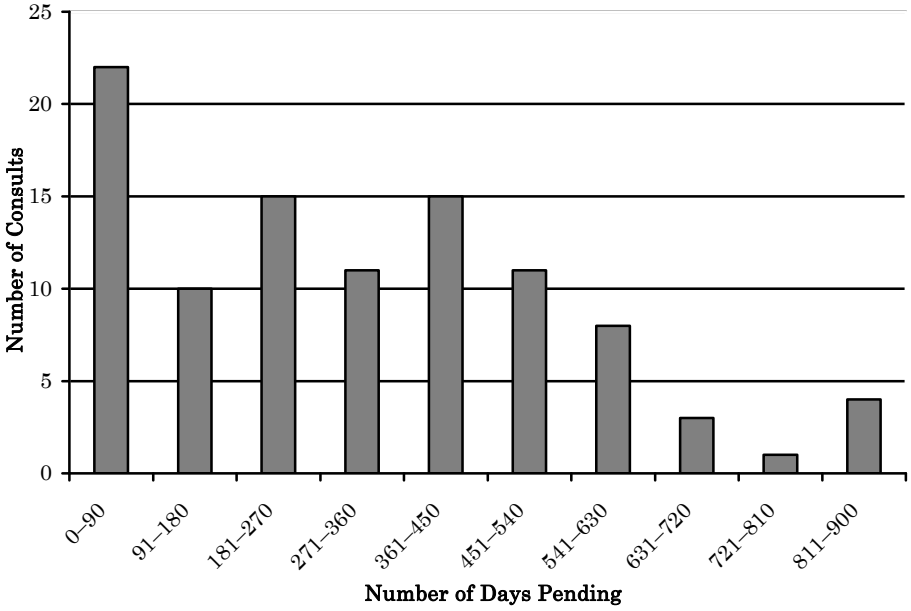
2006 Microbiology, Bioequivalence, and Labeling Review Time Ranges	
OGD Division	**Review Time Range for ANDAs With Review Time > 180 Days***
Microbiology	181–651 days
Bioequivalence	181–610 days
Labeling	181–627 days

* Review time ranges may be underestimated because review times for pending ANDAs in these divisions were accruing when we obtained the data. For ANDAs with review times greater than 180 days, the percentages that were pending at the time we obtained the data were: 73 percent for Microbiology (127 of 175 ANDAs), 3 percent for Bioequivalence (16 of 576 ANDAs), and 32 percent for Labeling (178 of 556 ANDAs).

Source: Office of Inspector General analysis of FDA COMIS data, 2007.

APPENDIX ~ D

Frequency Distribution of Office of Generic Drugs Consults Pending as of June 2007



Source: Office of Inspector General analysis of FDA's consult data, 2007.

APPENDIX ~ E

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

DATE: May 1, 2008

TO: Inspector General

FROM: Chief of Staff, FDA

SUBJECT: FDA's Comments on the Office of the Inspector General's Draft Report on the Generic Drug Review Process (OEI-04-07-00280)

Thank you for the opportunity to review and comment on the Office of the Inspector General's draft report for the Generic Drug Process (OEI-04-07-00280). The Food and Drug Administration has completed its review, and comments are attached.

If you need any additional information, please have one of your staff members contact Karen Bland-Vanison at (301) 827-6858.

Susan C. Winckler

Susan Winckler, RPh, Esq.

Attachment

Food and Drug Administration's Response to the Office of Inspector General (OIG) Draft Report on the Generic Drug Review Process (OEI-04-07-00280)

In preface to our comments, it is important to place review activities of the Office of Generic Drugs (OGD) in the context of the high numbers of original applications, amendments, supplements, annual reports as well as other review staff responsibilities, including guidance development and sponsor educational activities. The incoming workload has grown at a faster rate than the growth of OGD staff as the statements on pages iii and 7 – 8 illustrate. In addition, it should be noted that, historically, the review of abbreviated new drug applications (ANDA) was focused on the review of the chemistry manufacturing and controls (CMC) information and labeling conformance to the innovator product. The bioequivalence and microbiology reviews were consulted out of the Division of Generic Drugs (precursor to the Office of Generic Drugs) earlier in the program. Further, the official delegation of authority for 'not approving' ANDAs goes only to the Office Director and the Directors of the Divisions of Chemistry. That background may provide some rationale for the emphasis on the chemistry review in the overall process.

We are pleased to note that portions of the primary recommendations have already been identified by OGD and CDER staff and FDA is implementing process improvement activities that are the same or similar to the recommendations.

OGD Response to Recommendations:

Identify Common Original Abbreviated New Drug Application Deficiencies and Offer More Guidance to Industry to Decrease the Percentage Disapproved

This recommendation could be made clearer by adding that OGD should decrease the percentage disapproved "on the first cycle." Findings detailed in the report state that OGD approved or tentatively approved 4 percent of original ANDAs under review in 2006. As noted in the Technical Comments section below, this should be clarified by further stating there were 4 percent approved "on the first cycle." We agree that increasing the number of applications approved on the first cycle would help streamline the review process by decreasing the number of amendments and subsequent review cycles.

Over the years, various assessments of common deficiencies (particularly those noted in the initial filing review) in ANDAs have been done. OGD frequently participates in meetings, workshops, webcasts, and similar venues with the generic industry and foreign regulators to communicate information that sponsors may use to improve the quality of the applications, thus making them easier to review and more likely to be approved on the first cycle. For example, in 2008, there was a webinar with the Regulatory Affairs Professional Society in April, a labeling workshop with the Generic Pharmaceutical Association (GPhA) in May, a two-day workshop on communication jointly sponsored by FDA and the University of Rhode Island scheduled for the end of June, and there will

be a two-day technical workshop with the Generic Pharmaceutical Association (GPhA) in October.

We have found that larger more experienced firms have responded with high quality, complete, and more easily reviewed applications. Recently, however, there are increasing numbers of new, inexperienced firms submitting applications. Many will require a great deal of education even on the basic information necessary to be included in an ANDA.

The development of guidance is a continually evolving process due to the expansion of scientific knowledge and the impact of more complicated products being proposed as generic products. OGD is not always able to anticipate what products will be submitted for review and provide prospective guidance to firms. Currently, the Agency provides a number of guidance documents addressing chemistry, bioequivalence, microbiology and labeling, including a unique product-specific bioequivalence guidance which is updated periodically to add recommendations for additional products. These documents are available on the FDA website.

In addition, the Agency posts instructions and example documents for the new chemistry review paradigm, Question-based Review (QbR) on the FDA website. The QbR format tracks the Common Technical Document from the International Conference on Harmonization providing a consistent, more easily reviewed chemistry portion of an ANDA. Early indications are that the QbR can decrease review time. Example tables for display of bioequivalence data are also provided. We also provide guidance at the written request of potential sponsors whenever possible. All of these efforts assist industry to submit more easily reviewed applications.

Increase the Percentage of Original Abbreviated New Drug Applications Reviewed by All Divisions within 180 Days

To address review times on a broad basis, we have a focused hiring program to increase staff in critical review areas. Upon the completion of new reviewer training when the new staff become productive, it is anticipated review times will decrease.

OGD has assessed and continues to assess and alter its review processes with the goal of reducing overall queue time and completion of review within 180 days. With the increased staff, OGD will develop an additional bioequivalence review division, additional microbiology teams and additional chemistry review teams. Other approaches are being developed to increase review efficiency. For example, certain responsibilities have been identified that may be assumed by the Project Management staff. With such changes, additional reviewer time will be available for completion of scientific review. Through initiatives by the Office of Pharmaceutical Science (OPS), review of supplements is being streamlined based on a risk-based assessment of the changes proposed in the supplements. These endeavors to decrease the overall review responsibilities are expected to give reviewers additional time for review of original ANDAs decreasing queue times for those applications.

Identify New Prioritization Practices to Reduce Review Time for Abbreviated New Drug Applications Close to Approval

"Close to approval" is a relative term and cannot be easily defined due to the variety of external forces that affect the completion of review and potential approval of an application. Not only do consults, as identified by OIG, affect actions on applications, but citizen petitions, lawsuits, current Good Manufacturing Practices inspections of manufacturing facilities, the Division of Scientific Investigations inspections of bioequivalence study sites (especially foreign inspections), the individual firm's inspectional status (e.g., a negative Official Action Indicated), and new scientific or regulatory issues that may be identified during the course of review of the ANDA affect the potential time frame for approval. OGD may prioritize certain applications but then be stopped from taking action due to external factors that could not be predicted at the time the application was prioritized. Such a prioritization results in investing review effort without the expected gain.

Basing review priority on potential market entry date is already done to a certain extent. We currently expedite any application for a first generic product received in the office that has no patents or exclusivity on the corresponding reference product at the time of submission. These applications are for products that are likely to provide a lower-cost alternative promptly upon approval. Applications for generic versions of products that are due to have patents expire are generally ready for approval at the time those patents expire. There often, however, is no clear-cut date such as patent expiry with which to forecast likely market entry. Further, generic firms may or may not start marketing a product at the time of approval of the application depending upon ongoing litigation, settlement agreements, or corporate strategies and priorities.

OGD does attempt to re-prioritize review when most review disciplines find the application approvable. When the chemistry review of an ANDA is complete and approval is recommended, that application goes to the top of the queue in microbiology (if microbiology review is needed), labeling, and in the Division of Bioequivalence. This approach has been very successful in completing the review of applications in an expeditious manner. The Office successfully coordinates this endeavor through use of an "Approval Matrix" – a document updated on a regular basis that lists applications for which chemistry has recommended approval. In weekly "Approvals Meetings", the Project Managers from chemistry, bioequivalence, and microbiology review the listing to assure coordination of the re-prioritization and determine steps needed to bring the application to approval.

The recommendation to "classify amendments according to FDA policy and assign high priority to ANDAs with only minor deficiencies" is not clear in its intent. As noted above, due to the current workload, applications are prioritized for microbiology, labeling and bioequivalence review based upon a completed chemistry review recommending the approval of the ANDA. It does not appear that the classification of amendments in those review areas would have an overall effect on the completion of the review, especially

because the reviews in those areas take less time to complete than the chemistry reviews. Further, the accepted practice in OGD is that when a new bioequivalence study or similar "major" deficiency is found in another review discipline, the chemistry amendment is converted to a major amendment.

A possible consideration in terms of re-prioritization would be to delay review of applications that seek final approval only upon expiration of a patent far into the future. Such a process has not been fully explored and it would require thorough examination of all related issues as well as policy changes within OGD.

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