CY 2017 FDARA Section 902 Annual Report on Inspections

Facility Inspections Necessary to the Approval of Specified Human Drugs and Medical Devices

Acronyms

ANDA – Abbreviated New Drug Application

CBER – Center for Biologics Evaluation and Research

CDER – Center for Drug Evaluation and Research

CDRH – Center for Devices and Radiological Health

CGMP – Current Good Manufacturing Practice

CMC – Chemistry, Manufacturing, and Controls

CR – Complete Response

CY – Calendar Year

FDA – Food and Drug Administration

FD&C Act – Federal Food, Drug, and Cosmetic Act

FDARA – Food and Drug Administration Reauthorization Act of 2017

IA – Import Alert

NAI – No Action Indicated

NDA – New Drug Application

ORA – Office of Regulatory Affairs

OAI – Official Action Indicated

PAI – Pre-Approval Inspection

PMA – Pre-Market Approval

TPLC – Total Product Life Cycle

VAI – Voluntary Action Indicated

WL – Warning Letter

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Introduction

Background

On August 18, 2017, the Food and Drug Administration Reauthorization Act (FDARA) (Public Law 115-52) was signed into law. FDARA amends the Federal Food, Drug, and Cosmetic Act (FD&C Act) to revise and extend the use fee programs for drugs, medical devices, and biosimilar biological products, and for other purposes.

Section 902 of FDARA requires the Food and Drug Administration (FDA) to publicly report information related to inspections of facilities necessary for approval of a drug or a device. FDARA section 902 requires that the FDA make a report regarding facility inspections related to drug and device approvals available on an annual basis through the Agency's website. Section 902 of FDARA states:

> ANNUAL REPORT ON INSPECTIONS.
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> Not later than March 1 of each year, the Secretary of Health and Human Services shall post on the internet website of the Food and Drug Administration information related to inspections of facilities necessary for approval of a drug under section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355), approval of a device under section 515 of such Act (21 U.S.C. 360e), or clearance of a device under section 510(k) of such Act (21 U.S.C. 360(k)) that were conducted during the previous calendar year. Such information shall include the following:
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> (1) The median time following a request from staff of the Food and Drug Administration reviewing an application or report to the beginning of the inspection, and the median time from the beginning of an inspection to the issuance of a report pursuant to section 704(b) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 374(b)).
>
> (2) The median time from the issuance of a report pursuant to such section 704(b) to the sending of a warning letter [WL], issuance of an import alert [IA], or holding of a regulatory meeting for inspections for which the Secretary concluded that regulatory or enforcement action was indicated.
>
> (3) The median time from the sending of a warning letter [WL], issuance of an import alert [IA], or holding of a regulatory meeting to resolution of the regulatory or enforcement action indicated for inspections for which the Secretary concluded that such action was indicated.
>
> (4) The number of times that a facility was issued a report pursuant to such section 704(b) and approval of an application was delayed due to the issuance of a withhold recommendation.

FDA Interpretation

This report satisfies the annual reporting requirement set forth by FDARA section 902 for Calendar Year (CY) 2017. The report contains data on inspections necessary for the approval of specified human drugs and medical devices. FDA has interpreted FDARA section 902 as follows:

- With respect to drug-related inspections, section 902 is limited by its terms to information related to inspections of facilities necessary for approval of drugs under section 505 of the FD&C Act. Biological products, including biosimilars, approved under section 351 of the Public Health Service Act, are not included in this report.
- Section 902 is limited by its terms to information related to inspections of facilities. While in some cases approvals of drug products may be delayed because of inspections of sites at which bioavailability tests are performed or data from such tests are analyzed, the term "facility" is defined in section 744A(5) of the FD&C Act in a way that does not include such sites.
- Section 902 refers to information related to inspections of facilities necessary for approval of a drug. The FDA interprets the statute as requiring information not only with respect to approval of original new drug applications (NDA) or abbreviated new drug applications (ANDA) but also with respect to approval of supplements to such applications, including both prior approval supplements and changes being effected supplements.
- With respect to device-related inspections, section 902 is limited by its terms to information related to inspections of facilities necessary for approval of a device under section 515 of the FD&C Act or clearance of a device under section 510(k) of the FD&C Act.[1] Because humanitarian device exemptions are granted under section 520(m), information concerning humanitarian use devices is not included in this report. The FDA interprets the statute as requiring information not only with respect to approval of a premarket approval application, but also with respect to approval of supplements to such applications.
- Section 902 uses the term "report pursuant to section 704(b)." The FDA interprets this phrase to refer to Form FDA 483[2], Inspectional Observations, which is the list of observations made by FDA investigators during inspections that is left with the management of the inspected facility at the conclusion of the inspection. With the exception of the data reported in Tables 1 and 6 below, inspections not resulting in issuance of a Form FDA 483 are excluded from the analysis below.
- Section 902(1) refers to requests from staff of the FDA "reviewing an application." The FDA interprets this statutory provision to refer to staff at the reviewing Center at FDA.
- The FDA conducts different types of inspections of facilities in which a conclusion of lack of compliance may result in delay of approval of an application. The FDA conducts so-called "pre-approval inspections," but it also conducts inspections for other purposes, such as surveillance and for-cause inspections. Because a pre-approval inspection is requested by reviewing staff, the FDA interprets subsection 902(1) to apply to pre-

[1] However, clearance of a device under section 510(k) of the FD&C Act does not require a pre-clearance inspection and clearance is not withheld or delayed based on Form FDA 483 observations.
[2] More information about Form FDA 483 can be found at: www.fda.gov/ICECI/Inspections/ucm256377.htm

approval inspections. The result of a pre-approval inspection may be a decision that an application may not be approved, but a WL, issuance of an IA, or the holding of a Regulatory Meeting would follow other types of inspections rather than a pre-approval inspection. For that reason, the FDA interprets subsections 902(2) and (3) to apply to inspections other than pre-approval inspections. Because section 902 requires the FDA to provide information related to inspections of facilities necessary for approval of a drug or for approval or clearance of a device, the FDA reports under subsections 902(2) and (3) information concerning facilities that are referenced in a pending application. The FDA interprets subsection 902(4) to apply to both pre-approval inspections and other types of inspections. We note that by its terms section 902 is limited to information related to inspections "that were conducted during the previous calendar year." Thus, information reported with respect to subsections 902(2) and (3) does not include data concerning inspections that were conducted during prior calendar years that resulted in WLs, IAs, or Regulatory Meetings during CY 2017.

- Section 902(2) refers to Regulatory Meetings "for inspections for which the Secretary concluded that regulatory or enforcement action was indicated." The FDA understands this phrase to limit the reporting request to Regulatory Meetings based on inspections that FDA has classified as Official Action Indicated (OAI). We note that the FDA sometimes holds Regulatory Meetings with respect to facilities that it classifies as Voluntary Action Indicated (VAI) to discuss the proposed voluntary action, but such meetings are not included in the results reported here. In this report, accordingly, the term "Regulatory Meeting" refers to a meeting with respect to a facility that the FDA has classified as OAI.
- The FDA understands subsection 902(3) to apply, consistent with its terms, to inspections resulting in a WL, issuance of an IA, or the holding of a Regulatory Meeting. We note that there are, at least theoretically, situations in which a surveillance inspection would lead directly to a more serious enforcement action, such as a seizure, injunction, or prosecution, without a WL, IA, or Regulatory Meeting. Such rare circumstances, if they exist, would not be included.
- Subsection 902(4) refers to situations in which approval of an application was delayed due to the issuance of a withhold recommendation. The FDA interprets this provision as applying to those situations in which the "withhold recommendation" was because of the lack of compliance at the facility determined by a site inspection that resulted in a Form FDA 483 issuance at the close of the inspection. Thus, the FDA reports those situations in which the inspection of the facility is specifically used or cited as the only reason for delaying or denying approval. The FDA is not including in the report situations in which approval is denied or delayed for other reasons not related to inspections so that approval could not occur even if there were no inspection assessment findings.

Data Collection and Definitions

The FDA organizations[3] providing information for this Annual Report are:

- Center for Biologics Evaluation and Research (CBER);
- Center for Drug Evaluation and Research (CDER);
- Center for Devices and Radiological Health (CDRH); and
- Office of Regulatory Affairs (ORA).

Human Drugs Data

The data mandated under FDARA section 902 are summarized in five tables in the Human Drugs section.

Tables 1 and 2 respond to paragraph 1 of the statute. Table 1 reports the median time between the request of staff reviewing an application and the beginning of an inspection in CY 2017. Table 2 reports the median time between beginning of the inspections in Table 1 and the issuance of a Form FDA 483 for inspections completed in CY 2017.

Table 3 corresponds to paragraph 2 of the statute. The table reports the median time between Form FDA 483 issuance to the regulatory or enforcement action (i.e. WL, IA, or Regulatory Meeting) for Current Good Manufacturing Practice (CGMP) inspections that ended in CY 2017 and resulted in a WL, IA, or Regulatory Meeting pursuant to an issued Form FDA 483.

Table 4 corresponds to paragraph 3 of the statute and reports the median time between the initiation of a WL, IA, or Regulatory Meeting, and the resolution of the regulatory or enforcement action for CGMP inspections that ended in CY 2017 and resulted in a WL, IA, or Regulatory Meeting pursuant to an issued Form FDA 483.

Table 5 corresponds to paragraph 4. It reports on the number of applications that received a Complete Response (CR) letter delaying approval due to a facility withhold recommendation resulting from an inspection (i.e. pre-approval or surveillance CGMP inspection) that ended in CY 2017 where the inspection findings deficiency was the only deficiency cited in the CR letter. FDA is not including in the report situations where non-inspection assessment deficiencies were included in the CR letter in addition to inspection findings deficiencies.

[3] More information on the FDA product Centers and the Office of Regulatory Affairs can be found at: www.fda.gov/aboutFDA/Centersoffices/default.htm.

Medical Devices Data

The data mandated under FDARA section 902 are summarized in five tables in the Medical Devices section.[4]

Tables 6 and 7 respond to paragraph 1 of the statute. Table 6 reports the median time between the request of staff reviewing an application and the beginning of an inspection in CY 2017. Table 7 reports the median time between beginning of the inspection and the issuance of a Form FDA 483 for inspections completed in CY 2017.

Table 8 corresponds to paragraph 2 of the statute. The table reports the median time between the Form FDA 483 issuance to the regulatory or enforcement action (i.e. WL, IA, or Regulatory Meeting). The data include all inspections conducted in CY 2017 concluding with a Form FDA 483 at an establishment associated with a Pre-Market Approval (PMA) that resulted in the issuance of a WL, IA, or Regulatory Meeting in CY 2017.

Table 9 corresponds to paragraph 3 of the statute and reports the median time between the regulatory or enforcement action (i.e., WL, IA, or Regulatory Meeting) initiation and the resolution of that action for all inspections conducted in CY 2017 concluding with a Form FDA 483 at an establishment associated with a PMA that resulted in the issuance of a WL, IA, or Regulatory Meeting in CY 2017.

Table 10 corresponds to paragraph 4 of the statute and includes all PMA reviews that were stopped due to deficiencies found during CGMP compliance review documented on a Form FDA 483. This results in the FDA delaying decisions until the CGMP issues are resolved. This table includes inspections that ended in CY 2017 with the issuance of a Form FDA 483 and resulted in a delay of the PMA.

[4] Data include PMA approved medical devices involved in the manufacture of blood and human cell-based products.

Human Drugs

Median Time between Inspection Request and Beginning of Inspection

In CY 2017, the median time between an inspection request from FDA staff to the beginning of an inspection was 102 days (Table 1).

Table 1: Median Time between Inspection Request from FDA Staff Reviewing an Application or Report to the Beginning of the Inspection

Submission Type	CY 2017 Median Time (Calendar Days)
NDA & ANDA	102

Table 1 reports the median time in calendar days from Center's staff request for a pre-approval inspection (PAI) and the beginning of the inspection if ORA concurs with the inspection request. The data reported in Table 1 include all requests by reviewing staff where an inspection was initiated, even if no Form FDA 483 was issued at the conclusion of the inspection.

Median Time between Beginning of Inspection and Issuance of Form FDA 483 Report

In CY 2017, the median time between the beginning of a PAI to the issuance of a Form FDA 483 was seven days (Table 2).

Table 2: Median Time between Beginning of Inspection and Issuance of Form FDA 483 Report

Submission Type	CY 2017 Median Time (Calendar Days)
NDA & ANDA	7

Table 2 reports the median time in calendar days from the start of a PAI to the issuance of a Form FDA 483, which is also the date the inspection concludes. Inspections that have not resulted in a Form FDA 483 being issued are not included in this statistic.

Median Time between Issuance of Form FDA 483 Report to Regulatory or Enforcement Action

In CY 2017, the median time between the issuance of a Form FDA 483 and enforcement action was 191 days for WLs and 169 days for Regulatory Meetings (Table 3). There were no facilities added to an IA that were issued a Form FDA 483 for inspections occurring in CY 2017 which were classified final OAI and were named in a pending application.

Table 3: Median Time between Issuance of Form FDA 483 Report and Regulatory or Enforcement Action

Submission Type	CY 2017 Median Time FDA-483 to WL (Calendar Days)	CY 2017 Median Time FDA-483 to IA (Calendar Days)	CY 2017 Median Time FDA-483 to Regulatory Meeting (Calendar Days)
NDA & ANDA	191	--	169

Table 3 reports the median time in calendar days from the close of an inspection that resulted in the issuance of a Form FDA 483 to the initial enforcement action date, for each type of enforcement action specified in section 902 (i.e. WL, IA, and Regulatory Meeting). This report is limited to inspections that were issued a Form FDA 483 and that resulted in a WL, IA, or Regulatory Meeting. Data in this section are only reported for CGMP inspections because PAIs do not result in any of the above mentioned regulatory actions. The only CGMP inspections considered for this report are those associated with facilities that are referenced in a pending NDA or ANDA application with the FDA.

Median Time between Regulatory or Enforcement Action to Resolution of Regulatory or Enforcement Action

There were no resolutions for compliance actions for facilities that were issued a Form FDA 483 in CY 2017, that resulted in a WL, IA, or Regulatory Meeting, and were named in a pending application (Table 4).

Table 4: Median Time between Regulatory or Enforcement Action and Resolution

Submission Type	CY 2017 Median Time WL to WL Close Out (Calendar Days)	CY 2017 Median Time IA to IA Lift (Calendar Days)	CY 2017 Median Time Regulatory Meeting to OAI Downgrade (Calendar Days)
NDA & ANDA	--	--	--

Table 4 reports the median time in calendar days from initiation to resolution for each compliance action (i.e. WL, IA, and Regulatory Meeting) enumerated in section 902. This data consists of the median time from WL, IA, or Regulatory Meeting based on an inspection completed in CY 2017, to regulatory or enforcement action, and to resolution of that action. Resolution includes the firm addressing the OAI outcome, and re-inspection and classification of the site as VAI or No Action Indicated (NAI), if appropriate. We are reporting the median time in calendar days from initiation of a WL to close out of the WL; the median time from adding a

facility to an IA to the removal of that facility from the IA; and the median time from the date of a Regulatory Meeting to the reclassification of the site from OAI to VAI or NAI.

Significant remediation efforts by the site and subsequent re-inspection by the FDA are usually required to determine if the CGMP issues have been resolved at a site classified as OAI; therefore, it is unlikely that a site will be inspected and a regulatory action (i.e. WL, IA, or Regulatory Meeting) taken, and resolution completed within a single calendar year. Further, only inspections with a CGMP surveillance component are reported here, as purely pre-approval inspections do not result in any of the enumerated regulatory actions. Finally, only CGMP inspections associated with facilities that have a pending NDA or ANDA are reported here.

Application Delay due to Issuance of Withhold Recommendation

In CY 2017, 94 applications were denied approval solely due to a facility-related withhold recommendation (Table 5).

Table 5: Number of Times Application Approval was Delayed due to Withhold Recommendation

Submission Type	CY 2017 Count
NDA & ANDA	94[5]

Table 5 reports on the number of applications that were denied approval through the issuance of a CR letter due to a withhold recommendation because of the lack of compliance at a facility found during an inspection completed in CY 2017.[6] This report includes applications that received a CR letter only because a facility named in the application was determined not to be in compliance as a result of an FDA inspection. Applications with any other inadequacies beyond facility non-compliance observed during an inspection are not included in this report.

Applications with facility withhold recommendations due to inspections completed in years prior to CY 2017 are not reflected in this report. Facility issues that are not found during an inspection (i.e. those found during the assessment of the application and addressed by the application review process only, and facility issues that are found during an inspection but not included in a Form FDA 483) are not included in this count.

Only Chemistry, Manufacturing, and Controls (CMC) supplements are included in this data. Other supplement types were excluded because they do not routinely involve the assessment of facilities in determining approvability of the submission.

[5] A total of 2,461 CRs were issued in CY 2017 for Original Applications and CMC supplements. Of these 2,461 CRs, 288 CR actions were issued only due to a facility deficiency. Of the 288 CR actions that were issued only due to a facility deficiency, 94 CR actions were issued due to an inspection that occurred in CY 2017 and as described.
[6] CR letters identify all outstanding deficiencies that remain after a substantive review of the application and the application will not be approved until corrections as indicated are made.

Medical Devices

Median Time between Inspection Request and Beginning of Inspection

In CY 2017, the median time between an inspection request from FDA staff to the beginning of an inspection was 35 days (Table 6).

Table 6: Median Time between Inspection Request from FDA Staff Reviewing an Application or Report to the Beginning of the Inspection

Submission Type	CY 2017 Median Time (Calendar Days)
PMA	35

This median time reflects the median number of days between Center compliance staff requesting a PMA inspection and the beginning of the inspection by ORA. The beginning of the PMA inspection is the issuance of a Form FDA 482, Notice of Inspection. Form FDA 483 is issued at the close of an inspection only when the investigator(s) observed conditions that may constitute violations of the FD&C Act. The median time was influenced by factors such as ORA inspections that were conducted to cover more than one PMA or the state of the firm's readiness for inspection.

Median Time between Beginning of Inspection and Issuance of Form FDA 483 Report

In CY 2017, the median time between the beginning of a PMA inspection and the issuance of a Form FDA 483 was five days (Table 7).

Table 7: Median Time between Beginning of Inspection and Issuance of Form FDA 483 Report

Submission Type	CY 2017 Median Time (Calendar Days)
PMA	5

This median time reflects the median amount of days between the start of the PMA inspection, issuance of a Form FDA 482, and the issuance of a Form FDA 483. Form FDA 483 is issued at the close of an inspection only when the investigator(s) observed conditions that may constitute violations of the FD&C Act. This median excludes inspections that were closed when no Form FDA 483 was issued.

Median Time between Issuance of Form FDA 483 Report to Regulatory or Enforcement Action

During this CY 2017 reporting period, there were no instances of regulatory or enforcement actions (i.e. WL, IA, or Regulatory Meeting) resulting from a Form FDA 483 issued at establishments associated with a PMA submission. Therefore, a median time is not applicable.

Table 8: Median Time between Issuance of Form FDA 483 Report and Regulatory or Enforcement Action

Submission Type	CY 2017 Median Time (Calendar Days)
PMA	--

Median Time between Regulatory or Enforcement Action to Resolution of Regulatory or Enforcement Action

During this CY 2017 reporting period, there were no regulatory or enforcement actions (i.e. WL, IA, or Regulatory Meeting) at establishments associated with a PMA submission. Therefore, there are no regulatory or enforcement action resolutions.

Table 9: Median Time between Regulatory or Enforcement Action and Resolution

Submission Type	CY 2017 Median Time (Calendar Days)
PMA	--

Application Delay due to Issuance of Withhold Recommendation

The number of times that a PMA approval was withheld due to the issuance of a Form FDA 483 at the close of a PMA inspection in CY 2017 was five.

Table 10: Number of Times a Facility was Issued a Form FDA 483 and Application Approval was Delayed

Submission Type	CY 2017 Count
PMA	5

PMA approvals can be withheld in instances when ORA performed a PMA PAI and a Form FDA 483 was issued and resulted in a decision by the Center to withhold approval until the issues are resolved. Further, PMA approvals can be withheld in instances when ORA performed a non-PMA inspection and a Form FDA 483 was issued and resulted in a decision by the Center to withhold approval until the issues are resolved. Delays related to both PMA inspections and non-PMA inspections are included in Table 10.

Department of Health and Human Services
Food and Drug Administration

This report was prepared by FDA's Office of Planning with the Center for Biologics Evaluation and Research (CBER), Center for Drug Evaluation and Research (CDER), Center for Devices and Radiological Health (CDRH), and the Office of Regulatory Affairs (ORA). For information on obtaining additional copies contact:

Office of Planning
Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, Maryland 20993-0002
Phone: 301-796-4850

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