CY 2018

FDARA Section 902 Annual Report on Inspections

Facility Inspections Necessary for 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 – FDA 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 FDA Reauthorization Act of 2017 (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 user 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.
>
> Not later than March 1 of each year, the Secretary of Health and Human Services shall post on the internet website of the FDA 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:
>
> (1) The median time following a request from staff of the FDA 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, issuance of an import alert, 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, 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) 2018. 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(6) 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,

[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. Therefore, information regarding clearance of a device under section 510(k) of the Act will not be shown in the tables below.
[2] More information about Form FDA 483 can be found at: www.fda.gov/ICECI/Inspections/ucm256377.htm

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-approval inspections. The result of a pre-approval inspection may be a decision that an application is not approved; however, a warning letter (WL), issuance of an import alert (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.

- By its terms section 902 is limited to information related to inspections "that were conducted during the previous calendar year." However, actions reported with respect to subsections 902(2), (3), and (4) can take more than one year to occur, so the data concerning WLs, IAs, or Regulatory Meetings during CY 2018, resolutions of previous actions during CY 2018, or application delays due to issuance of withhold recommendations in CY 2018 are included in this report even though in some cases they reflect actions related to inspections conducted in 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). 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. There are 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 will 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 2018. Table 2 reports the median time between the beginning of the inspection and the issuance of a Form FDA 483 for inspections completed in CY 2018.

Table 3 corresponds to paragraph 2 of the statute. The table reports the median time between the Form FDA 483 issuance and the regulatory or enforcement action (i.e., WL, IA, or Regulatory Meeting). The data include all Current Good Manufacturing Practice (CGMP) inspections conducted in CY 2017 or 2018 that concluded with a Form FDA 483 and resulted in a WL, IA, or Regulatory Meeting in CY 2018.

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. This table includes all WL, IA, and Regulatory Meetings resolved in CY 2018, even if the WL, IA, or Regulatory Meeting was initiated in CY 2017.

Table 5 corresponds to paragraph 4 of the statue. It reports on the number of applications that received a Complete Response (CR) letter delaying approval due to a facility withhold recommendation in CY 2018 resulting from an inspection that ended in CY 2017 or CY 2018 with the issuance of a Form FDA 483 where the inspection findings deficiency was the only deficiency cited in the CR letter and resulted in the delay of approval.

[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 2018. Table 7 reports the median time between the beginning of the inspection and the issuance of a Form FDA 483 for inspections completed in CY 2018.

Table 8 corresponds to paragraph 2 of the statute. The table reports the median time between the Form FDA 483 issuance and the regulatory or enforcement action (i.e., WL, IA, or Regulatory Meeting). The data include all inspections conducted in CY 2017 or CY 2018 that concluded with a Form FDA 483 at an establishment associated with a Pre-Market Approval (PMA) and resulted in a WL, IA, or Regulatory Meeting in CY 2018.

Table 9 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. This table includes all WL, IA, and Regulatory Meetings resolved in CY 2018, even if the WL, IA, or Regulatory Meeting was initiated in CY 2017.

Table 10 corresponds to paragraph 4 of the statute. It reports on the number of PMA reviews that were stopped due to deficiencies from an inspection that ended in CY 2017 or CY 2018 with the issuance of a Form FDA 483 and resulted in a delay of the PMA in CY 2018.

[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 2018, the median time between an inspection request from FDA staff to the beginning of an inspection was 90 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 2018 Median Time (Calendar Days)	Number of inspections included in analysis
NDA & ANDA	90	225

Table 1 reports the median time in calendar days between a Center staff request for a pre-approval inspection (PAI) and the beginning of the inspection by ORA. The data reported in Table 1 includes 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

In CY 2018, the median time between the beginning of a PAI and the issuance of a Form FDA 483 was five days (Table 2).

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

Submission Type	CY 2018 Median Time (Calendar Days)	Number of inspections included in analysis
NDA & ANDA	5	112

Table 2 reports the median time in calendar days from the start of a PAI to 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. 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 to Regulatory or Enforcement Action

In CY 2018, the median time between issuance of a Form FDA 483 (which may have been the result of an inspection in the previous calendar year) and enforcement action was 242.5 days for WLs, 119 days for Import Alerts, and 154 days for Regulatory Meetings (which were classified OAI) for facilities that were named in a pending application (Table 3).

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

Submission Type	Median Time FDA 483 to WL (Calendar Days)	Median Time FDA 483 to IA (Calendar Days)	Median Time FDA 483 to Regulatory Meeting (Calendar Days)	Number of actions included in analysis
NDA & ANDA	242.5	119	154[5]	34

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 statistic 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

In CY 2018, there were no resolutions for regulatory or enforcement actions for facilities that were issued a Form FDA 483 between 1/1/2017 and 12/31/2018 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	Median Time WL to WL Close Out (Calendar Days)	Median Time IA to IA Lift (Calendar Days)	Median Time Regulatory Meeting to OAI Downgrade (Calendar Days)	Number of actions included in analysis
NDA & ANDA	--	--	--	--

Table 4 reports the median time in calendar days for firms cited in compliance actions enumerated in section 902 (i.e., WL, IA, and Regulatory Meeting) to remediate CGMP issues at a site classified as OAI, including the time for FDA to re-inspect the facility to confirm whether adequate remediation has, indeed, taken place. The compliance action is considered "initiated" the day the WL or IA is issued or the day the Regulatory Meeting takes place. The compliance action is considered "resolved" when the firm has addressed the violations or deviations sufficiently to allow the site to be reclassified by FDA as VAI or No Action Indicated (NAI), and, in the case of an IA or a WL, the Agency has also removed the facility from the IA or closed the WL.

Significant remediation efforts by the firm to resolve the CGMP issues at a site classified as OAI and subsequent re-inspection by the FDA to determine if the CGMP issues have been resolved

[5] Note, this excludes Regulatory Meetings held after a Warning Letter or similar compliance action has occurred, where the purpose of the regulatory meeting typically is to discuss the adequacy of the firm's response to the compliance action.

are usually required before reclassification. It is unlikely that a site will be inspected, a regulatory action (i.e., WL, IA, or Regulatory Meeting) taken, and resolution completed within a single calendar year. In some instances, firms either chose to not remediate, or never adequately remediate, CGMP issues observed at their facilities and compliance actions remain open indefinitely. Further, only inspections with a CGMP surveillance component are reported here, as pre-approval inspections do not result in any of the applicable regulatory actions. Finally, only CGMP inspections associated with facilities that were named in a pending NDA or ANDA are reported here.

Application Delay due to Issuance of Withhold Recommendation

In CY 2018, 115 applications were delayed solely due to a facility-related withhold recommendation (Table 5). This equates to less than 4 percent of the 3,015 CRs issued in CY 2018.

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

Submission Type	CY 2018 Count
NDA & ANDA	115[6]

Table 5 reports on the number of applications that were delayed 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 between 1/1/2017 and 12/31/2018. 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. 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.

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. Additionally, 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.

[6] A total of 3,015 CRs were issued in CY 2018 for Original Applications and CMC supplements. Of these 3,015 CRs, 141 CR actions were issued only due to a facility deficiency. Of the 141 CR actions that were issued only due to a facility deficiency, 115 CR actions were issued due to an inspection that occurred in CY 2017 and CY 2018.

Medical Devices

Median Time between Inspection Request and Beginning of Inspection

In CY 2018, the median time between an inspection request from FDA staff to the beginning of an inspection was 41 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 2018 Median Time (Calendar Days)	Number of inspections included in analysis
PMA	41	76

Table 6 reports the median time in calendar days between a Center review staff request for a PMA inspection and the beginning of the inspection by ORA. The data reported in Table 6 includes 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

In CY 2018, the median time between the beginning of a PMA inspection and the issuance of a Form FDA 483 was three days (Table 7).

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

Submission Type	CY 2018 Median Time (Calendar Days)	Number of inspections included in analysis
PMA	3	26

Table 7 reports the median time in calendar days from the start of the PMA inspection to 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. 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 to Regulatory or Enforcement Action

In CY 2018, there were no instances of an WL, IA, or Regulatory Meeting resulting from a Form FDA 483 issued (which may have been the result of an inspection in the previous calendar year) at establishments associated with a PMA submission. Therefore, a median time is not applicable (Table 8).

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

Submission Type	Median Time FDA 483 to WL (Calendar Days)	Median Time FDA 483 to IA (Calendar Days)	Median Time FDA 483 to Regulatory Meeting (Calendar Days)	Number of actions included in analysis
PMA	--	--	--	--

Table 8 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 statistic is limited to inspections that were issued a Form FDA 483 and that resulted in a WL, IA, or Regulatory Meeting.

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

In CY 2018, there were no resolutions for regulatory or enforcement actions for facilities that were issued a Form FDA 483 between 1/1/2017 and 12/31/2018 that resulted in a WL, IA, or Regulatory Meeting, and were named in a pending PMA application (Table 9).

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

Submission Type	Median Time WL to WL Close Out (Calendar Days)	Median Time IA to IA Lift (Calendar Days)	Median Time Regulatory Meeting to OAI Downgrade (Calendar Days)	Number of actions included in analysis
PMA	--	--	--	--

Table 9 reports the median time in calendar days from initiation to resolution in CY 2018 for each compliance action (i.e., WL, IA, and Regulatory Meeting) enumerated in section 902. 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. This includes 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 firm 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, which is why further information on resolutions from CY 2017 inspections are being provided with the CY 2018 information.

Application Delay due to Issuance of Withhold Recommendation

In CY 2018, there were two PMA approvals delayed due to the issuance of a Form FDA 483 at the close of an inspection (Table 10).

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

Submission Type	CY 2018 Count
PMA	2

Table 10 reports on the number of applications that were delayed due to the issuance of a Form FDA 483 at the close of inspections completed between 1/1/2017 and 12/31/2018. 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.

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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