Postmarketing Studies and Clinical Trials: Determining Good Cause for Noncompliance with Section 505(o)(3)(E)(ii) of the Federal Food, Drug, and Cosmetic Act

Guidance for Industry

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

July 2023
FDA Amendments Act (FDAAA)

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This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance provides information for holders of applications for human prescription drugs[2] (hereafter *applicants*) who are required to conduct postmarketing studies or clinical trials under section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (FD&C Act).[3] These postmarketing studies and clinical trials are also commonly referred to as postmarketing requirements (PMRs), or 505(o)(3) PMRs (hereafter *PMRs*). An applicant required to conduct a PMR under section 505(o)(3) must provide certain information to FDA, including a timetable for study or clinical trial completion and periodic reports on the status of the study or clinical trial. If an applicant fails to comply with the timetable or other requirements of section 505(o)(3)(E)(ii), the applicant is in violation of section 505(o)(3), unless the applicant has demonstrated *good cause* for its noncompliance or other violation.[4]

This guidance describes factors FDA considers when determining whether an applicant has demonstrated good cause for its noncompliance with the timetable for completion of PMR milestones[5] as required under section 505(o)(3). This guidance also provides information on relevant procedures including how to communicate with FDA regarding PMR compliance,

[1] This guidance has been prepared by a multidisciplinary work group, comprising staff from the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration.

[2] For the purposes of this guidance, all references to *drugs* include both human drugs and biological drug products regulated by CDER and CBER unless otherwise specified.

[3] The Food and Drug Administration Amendments Act of 2007 (FDAAA) added section 505(o) to the FD&C Act.

[4] Section 505(o)(3)(E)(ii) of the FD&C Act.

[5] For purposes of this guidance, milestones dates are a series of goal dates (e.g., final protocol submission, study or clinical trial completion date, final report submission) by which FDA measures progress of studies and clinical trials and compliance with requirements.

submission of an explanation of the circumstances that led to noncompliance, and how FDA notifies an applicant of a determination of noncompliance. Although this guidance primarily addresses noncompliance with the timetable for completion of PMR milestones, any violation of a requirement under section 505(o)(3)(E)(ii) of the FD&C Act is subject to enforcement action, in the absence of a demonstration of good cause.[6]

This guidance refers *only* to PMRs required under section 505(o)(3) of the FD&C Act. This guidance does not apply to the following types of PMRs:

- Pediatric studies required under section 505B of the FD&C Act (see 21 CFR 314.55(b) and 601.27(b)).
- Trials required as a condition of accelerated approval under section 506(c) of the FD&C Act and accelerated approval regulations (21 CFR 314.510 and 601.41).
- Trials required as a condition of approval based on evidence of effectiveness from studies in animals under subpart I of 21 CFR 314 (21 CFR 314.610(b)(1)) and subpart H of 21 CFR 601 (21 CFR 601.91(b)(1)).

This guidance does not apply to nonprescription drugs, including nonprescription drugs that are approved under a new drug application, or to generic drugs approved under section 505(j) of the FD&C Act. Section 505(o) of the FD&C Act applies only to prescription drugs approved under section 505(b) and biological drug products approved under section 351 of the Public Health Service Act (PHS Act).[7]

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

[6] In addition to a timetable for completion, section 505(o)(3)(E)(ii) of the FD&C Act includes requirements for periodic reports on the status of a study required under section 505(o)(3) or otherwise undertaken by the responsible person to investigate a safety issue, including whether any difficulties in completing the study have been encountered. Section 505(o)(3)(E)(ii) also includes requirements for periodic reports on the status of clinical trials required under section 505(o)(3) or otherwise undertaken by the responsible person to investigate a safety issue, including whether enrollment has begun, the number of participants enrolled, the expected completion date, whether any difficulties completing the clinical trial have been encountered, and registration information with respect to the requirements under section 402(j) of the Public Health Service Act (PHS Act) (42 U.S.C. 282(j)).

[7] See section 505(o)(2)(B) of the FD&C Act.

II. BACKGROUND

Section 505(o)(3) of the FD&C Act authorizes FDA to require certain postmarketing studies and clinical trials[8] for prescription drugs at the time of approval or after approval if FDA becomes aware of *new safety information*.[9] Section 505(o)(3)(E) requires an applicant to provide certain information to FDA about its PMR, including a timetable for study or clinical trial completion and periodic reports on the status of the study or clinical trial. PMR milestones are in the timetable to measure the progress of studies and clinical trials. A timetable with milestone dates is usually proposed by the applicant, and the FDA review team assesses whether the proposed timetable will provide for timely completion of the study or clinical trial. Once milestones are agreed upon, they are included in the action letter or postapproval letter acknowledging new PMRs. This original timetable serves as the basis for determining the status of the PMR,[10] even if the applicant subsequently proposes a revised timetable.[11] The milestones generally include, but are not limited to, the following:

(i) The final protocol submission date — the date by which the applicant submits a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised and submitted as needed to meet the goal of the study or clinical trial.[12]

(ii) The study or clinical trial completion date — the date the last subject who enrolled in the study or clinical trial completes the last (per protocol) observation or evaluation.

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[8] See the draft guidance for industry *Postmarketing Studies and Clinical Trials — Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (Revision 1)* (October 2019) for FDA's definitions of *clinical trials* and *studies* for purposes of implementing section 901 of FDAAA. When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[9] See section 505-1(b)(3) of the FD&C Act for the definition of the term *new safety information*. See the draft guidance for industry *Postmarketing Studies and Clinical Trials — Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (Revision 1)* for discussion of this term. When final, this guidance will represent the FDA's current thinking on this topic.

[10] See 21 CFR 314.81(b)(2)(vii)(a)(8) and the FDA's Postmarketing Requirements and Commitments: Status and Fulfillment Categories web page available at https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PostmarketingPhaseIVCommitments/ucm070799.htm.

[11] 21 CFR 314.81(b)(2)(vii)(a)(8) and 601.70(b)(8). Also, see the guidance for industry *Reports on the Status of Postmarketing Study Commitments — Implementation of Section 130 of the Food and Drug Administration Modernization Act of 1997* (February 2006).

[12] The date for this milestone should be selected to allow for the discussion period needed to create a well-designed study or clinical trial. See the draft guidance for industry *Postmarketing Studies and Clinical Trials – Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (Revision 1).* When final, this guidance will represent the FDA's current thinking on this topic.

(iii) The final report submission date — the date by which the applicant submits a complete study or clinical trial report to FDA.

A PMR timetable may include additional milestones, including interim milestones.

Section 505(o)(3)(E)(ii) of the FD&C Act requires an applicant to periodically report on the status of each PMR.[13] To comply with section 505(o)(3)(E)(ii), the applicant must also report on the status of any other study or clinical trial undertaken to investigate a safety issue. Except when otherwise provided, FDA considers the submission of the annual report required under 21 CFR 314.81 or 21 CFR 601.70, as applicable, as satisfying this periodic reporting requirement, if the required elements of information about the status of the PMR set forth in 505(o)(3)(E)(ii) are included in that report.[14]

If an applicant fails to meet one or more of the milestones specified in the timetable or fails to submit periodic reports on the status of the PMR(s), FDA considers the applicant to be in violation of section 505(o)(3) of the FD&C Act, unless the applicant has demonstrated good cause for its PMR noncompliance. Under section 505(o)(3)(E)(ii), FDA is responsible for determining what constitutes good cause for PMR noncompliance. FDA makes this determination by evaluating an applicant's explanation of the circumstance(s) that led to the noncompliance and any other information deemed pertinent. Violations of requirements under section 505(o)(3)(E)(ii) are subject to enforcement action, including pursuant to sections 505(o)(1) (charges under section 505 of the FD&C Act), 502(z) (21 U.S.C. 332(z)) (misbranding charges), and 303(f)(4)(A) (21 U.S.C. 333(f)(4)(A)) (civil monetary penalties).[15] Advisory[16] and

[13] Section 505(o)(3)(E)(ii) also requires that applicants report on the registration information for each clinical trial PMR with respect to the requirements under section 402(j) of the PHS Act. See the guidance for sponsors, industry, researchers, investigators, and FDA staff *Form FDA 3674 — Certifications to Accompany Drug, Biological Product, and Device Applications/Submissions* (June 2017). Section 402(j) of the PHS Act requires an applicant to submit additional information to the clinical trials data bank (available at https://www.ClinicalTrials.gov) and requires drug applications or submissions to include a certification that all applicable requirements have been met. An applicant can meet this requirement by submitting FDA Form 3674, which will also satisfy the registration information requirement under section 505(o)(3)(E)(ii) of the FD&C Act.

[14] With regard to studies, section 505(o)(3)(E)(ii) requires applicants to periodically report on the status of the study, including whether any difficulties in completing the study have been encountered. With regard to clinical trials, section 505(o)(3)(E)(ii) requires applicants to periodically report on the status of the trial, including whether enrollment has begun, the number of participants enrolled, the expected completion date, and whether any difficulties completing the clinical trial have been encountered. This information is generally included in the annual report required under 21 CFR 314.81 or 21 CFR 601.70. For further information refer to the draft guidance for industry *Postmarketing Studies and Clinical Trials — Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (Revision 1)*. When final, this guidance will represent the FDA's current thinking on this topic.

[15] In determining the amount of a civil monetary penalty, FDA takes into consideration whether the responsible person is making efforts toward correcting the violation.

[16] An advisory action communicates the FDA's position on a matter but does not commit FDA to taking enforcement action. FDA considers a warning or untitled letter to be informal and advisory. An enforcement action may include issuance of civil monetary penalties, misbranding charges, and charges under section 505 of the FD&C Act. See sections 303(f)(4)(A) and 502(z) of the FD&C Act. See the FDA's Regulatory Procedures Manual available at https://www.fda.gov/iceci/compliancemanuals/regulatoryproceduresmanual/default.htm.

enforcement actions are more fully discussed below (see section V., FDA Action for PMR Noncompliance).

III. DETERMINING GOOD CAUSE AND FAILURE TO DEMONSTRATE GOOD CAUSE FOR PMR NONCOMPLIANCE

A. Determining Good Cause for PMR Noncompliance

To determine whether an applicant has demonstrated good cause for PMR noncompliance, FDA evaluates the applicant's explanation of the circumstance(s) that led to the noncompliance (i.e., that caused the noncompliance). If an applicant fails to provide an explanation for PMR noncompliance, including lack of response to a direct inquiry from FDA, in general, FDA will consider the applicant to have failed to demonstrate good cause for the PMR noncompliance.

FDA intends to make a finding of good cause when an applicant's explanation for PMR noncompliance demonstrates that the noncompliance is reasonable under the circumstances. In general, FDA considers PMR noncompliance to be reasonable when it results from circumstances that meet the following criteria:

- The circumstance is directly related to the missed milestone;

  AND

- The circumstance was out of the applicant's control;

  AND

- The circumstance could not have been reasonably anticipated and factored in at the time the original PMR timetable was finalized.

In determining whether PMR noncompliance is reasonable under the circumstances, FDA may also consider any other available information that it deems pertinent.

If any one of the aforementioned conditions is not met, in general, FDA will consider the noncompliance to not be reasonable under the circumstances and the applicant as failing to demonstrate good cause for the noncompliance.

FDA will notify the applicant in writing of the determination of whether the applicant demonstrated good cause or failed to demonstrate good cause for PMR noncompliance.

The applicant could be subject to a warning letter followed by enforcement action for PMR noncompliance. FDA generally intends to assess the applicant's efforts to mitigate or correct the underlying cause(s) of the PMR noncompliance when considering advisory or enforcement action (see section V., FDA Action for PMR Noncompliance).

B. Examples of PMR Noncompliance FDA Would or Would Not Consider Reasonable Under the Circumstances

The following are examples of PMR noncompliance FDA generally would or would not consider reasonable under the circumstances. The following examples are for illustrative purposes only and are not exhaustive:

1. Missed Final Protocol Submission Milestone

PMR noncompliance associated with failure to submit a final protocol that FDA likely would find reasonable under the circumstances includes the following:

- Submission of a well-organized and complete protocol in advance of the milestone, followed by delayed FDA concurrence with the protocol resulting in the applicant missing the deadline for the final protocol submission. The delay is attributed to causes within FDA (e.g., ongoing internal scientific deliberations between FDA disciplines about key protocol issues; delayed communication to the applicant regarding FDA's recommendations for the final protocol; or changes in regulatory policy since the PMR was required that prohibit protocol development or initiation, such as substantial revision of guidance on how to conduct a particular study or clinical trial specified in the original PMR).

- Delay in finalizing a protocol because a particular aspect of the study or clinical trial is dependent upon the results of a prerequisite investigation for which there are justifiable delays in initiating or completing the investigation or interpreting the results. For example, the final protocol submission is delayed:

  - Because the subsequent clinical trial depends on the results of a dose-finding trial that is incomplete or

  - Because an assay that is critical to the design elements of the prerequisite study or clinical trial is unavailable

PMR noncompliance associated with failure to submit a final protocol that FDA likely would not find reasonable under the circumstances includes the following:

- Delays in manufacturing or launch of the drug, or other reasons for nonavailability of the drug, that do not affect the applicant's ability to write a protocol.

- Submission of a proposed protocol that FDA considers unlikely to provide meaningful data about the safety issues or questions the PMR was intended to address.

- Delayed response or lack of response by the applicant to FDA concerns or recommendations regarding the proposed protocol.

- Applicant's request to FDA to renegotiate the previously issued PMR (e.g., renegotiate the previously agreed-upon final study or clinical trial design), in the absence of critical new information making changes necessary.

- Applicant's assertion that it lacked knowledge of the requirement for a postmarketing study or clinical trial and/or lack of responsibility for the PMR because the drug application is now held by a new company that purchased the drug and assumed responsibility for the application.

- Applicant's assertion that the study or clinical trial design, as specified in the PMR, cannot be performed because of resource constraints (for instance, cost, labor, allocation of resources, or time).

2. Missed Study/Clinical Trial Completion Milestone

PMR noncompliance associated with failure to complete a study or clinical trial that FDA likely would find reasonable under the circumstances includes the following:

- Significant difficulties that are out of the applicant's control and could not have been anticipated and planned for with regard to subject recruitment for studies or clinical trials, including, for example, challenges in recruitment of individuals for reasons such as the following:

  - Adverse reactions of the drug added to the product labeling and/or the informed consent document for the study or clinical trial after a PMR was required that make subject enrollment in a clinical trial of the drug more difficult.

  - The availability of a new alternative therapy after an applicant's PMR was required that affects usage of the applicant's drug.

- Unanticipated drug access issues or foreign agency restrictions, such as the following:

  - Unexpected disruption or interruption in the supply (e.g., drug shortage, drug discontinuation) of the applicant's drug that is out of the applicant's control and delays the conduct of the study or clinical trial.

  - Drug importation or other unexpected access issues that affect the applicant's ability to obtain a necessary comparator drug for the study or clinical trial.

PMR noncompliance associated with failure to complete a study or clinical trial that FDA likely would not find reasonable under the circumstances includes the following:

- Inadequate subject recruitment for studies or clinical trials for which difficulties in subject enrollment should be unlikely (e.g., recruitment of healthy subjects for a drug-drug interaction trial or pharmacokinetics trial).

- Failure to complete prespecified and feasible interim data analyses that are considered relevant to inform appropriate completion of the study or clinical trial.

3. Missed Final Report Submission Milestone

PMR noncompliance associated with failure to submit a final report that FDA would likely find reasonable under the circumstances includes the following:

- Unanticipated drug access issues or foreign agency restrictions that affect the applicant's ability to complete the study or clinical trial and that subsequently interfere with the applicant's ability to submit a final report by the milestone.

PMR noncompliance associated with failure to submit a final report that FDA likely would not find reasonable under the circumstances includes the following:

- Responsible employee(s) have left the applicant's firm.

- Delayed routine data analysis of completed study or clinical trial results.

- Submission of other data in lieu of a final report that the applicant believes will satisfy the PMR milestone(s) but FDA finds inadequate to address the serious risk that prompted the PMR.

IV. PROCEDURES

A. Reporting on the Status of a PMR

Section 505(o)(3)(E)(ii) of the FD&C Act requires periodic reporting on the status of each study or clinical trial required under section 505(o)(3), including reporting on whether the applicant has encountered any difficulties completing the study or clinical trial. In addition, PMRs required under section 505(o)(3) are also subject to the reporting requirements of section 506B of the FD&C Act, as well as 21 CFR 314.81(b)(2)(vii) or 21 CFR 601.70.[17] As described in section II., Background, FDA considers the submission of the annual report required under 21 CFR 314.81(b)(2)(vii) or 21 CFR 601.70, as applicable, containing all of the elements set forth in 505(o)(3)(E)(ii) as satisfying the periodic reporting requirement under section 505(o)(3)(E)(ii).

[17] Under these sections of the statute and regulations, applicants are required to submit annual reports on the status of any PMR/PMC studies or clinical trials. These annual reports should include the original milestones, current status of the study or clinical trial, an explanation of the progress of the study or clinical trial, any revised milestones, and the reasons for the revisions. See the guidance for industry *Reports on the Status of Postmarketing Study Commitments — Implementation of Section 130 of the Food and Drug Administration Modernization Act of 1997* and the draft guidance for industry *Postmarketing Studies and Clinical Trials — Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (Revision 1)*. When final, this guidance will represent the FDA's current thinking on this topic.

B. Submitting an Explanation for PMR Noncompliance or Anticipated Noncompliance

Because the required milestone may occur far in advance of the required periodic updates that are generally submitted in an annual report, FDA strongly encourages applicants to proactively inform FDA about the progress and status of their PMR(s). If an applicant anticipates missing a milestone or has already missed the milestone and submission of an annual report is not imminent, FDA encourages the applicant to notify FDA as soon as possible of the delay and submit thorough explanations of the failure to meet the PMR milestones. Applicants who have a revised PMR timetable who fail or anticipate failing to meet any of the revised milestones should also submit an explanation for FDA to evaluate. As more fully discussed below, applicants who miss (or anticipate missing) PMR milestones should promptly implement the appropriate actions that are necessary to correct the underlying circumstance(s) of the PMR noncompliance and include a description of these actions in the explanation for PMR noncompliance.

FDA determines whether an applicant has demonstrated good cause for noncompliance with a PMR milestone in the timetable only after the applicant has missed the milestone date. FDA recognizes, however, that an applicant can often know in advance that a milestone may be missed, proactively notify FDA of the anticipated missed milestone, and provide an explanation for the anticipated delay. Before the applicant misses a milestone, FDA can assess whether it finds that the applicant has provided sufficient justification for the anticipated delay (i.e., anticipated failure to meet a future milestone). FDA plans to notify an applicant of its determination that an applicant has failed to provide *sufficient justification* for the *anticipated* delay in meeting the PMR milestone.

Applicants should identify their submitted explanations for actual or anticipated PMR delay with the following wording in bold capital letters on the top of the first page of the submission: "Notification of Failure to Meet a PMR Milestone(s) Required Under Section 505(o)" or "Notification of Anticipated Failure to Meet a PMR Milestone(s) Required Under Section 505(o)."

C. Actions Taken to Correct Circumstances That Led to PMR Noncompliance

After a missed milestone, or other PMR noncompliance, FDA reviews the explanation provided to determine whether the applicant has demonstrated that it has undertaken appropriate action to correct or mitigate the circumstance that led to the PMR noncompliance. The appropriateness of these actions depends on the type of milestone and the circumstances underlying the PMR noncompliance. However, in general, FDA considers an applicant to have undertaken appropriate action if the applicant does the following:

- Promptly[18] develops and implements a reasonable plan to correct the underlying circumstance(s) leading to the PMR noncompliance;

[18] FDA determines an applicant's promptness based on the specific circumstance and on a case-by-case basis.

- Proactively informs FDA of actual or anticipated delays and the plan to correct the underlying circumstance(s) leading to the PMR noncompliance; and

- Proposes a reasonable revised timetable.

FDA may consider multiple episodes of an applicant's failure to meet a PMR milestone in determining whether the applicant has undertaken appropriate action to correct or mitigate the circumstance that led to PMR noncompliance. FDA intends to consider whether the applicant has taken appropriate actions to correct the circumstances that led to PMR noncompliance when considering advisory or enforcement action.

V. ADVISORY OR ENFORCEMENT ACTION FOR PMR NONCOMPLIANCE

Applicants are subject to advisory or enforcement action for any of the following violations of section 505(o)(3)(E)(ii) of the FD&C Act unless the applicant has demonstrated good cause for noncompliance:

- Failure to meet a milestone in the PMR timetable[19]

- Violation of any other requirement under section 505(o)(3)(E)(ii) of the FD&C Act, including failure to periodically report on the status of each required postmarketing study or clinical trial through the submission of a PMR status report in an annual report or by other means[20]

Examples of advisory and enforcement actions include the following:

- Issuance of a warning or untitled letter. FDA issues warning letters to applicants to achieve voluntary compliance before taking enforcement action. An untitled letter cites violations that do not meet the threshold of regulatory significance for a warning letter.[21]

- Misbranding charges. A drug is misbranded under section 502(z) of the FD&C Act (21 U.S.C. 352(z)) if the responsible person[22] is in violation of postmarketing study or clinical trial requirements established under section 505(o)(3) of the FD&C Act. The introduction or delivery for introduction into interstate commerce of a misbranded product violates section 301(a) of the FD&C Act. It is also a prohibited act under section

[19] If FDA determines an applicant has demonstrated good cause for missing a milestone in the original PMR timetable, FDA will monitor for the applicant's compliance with the proposed revised timetable (as acknowledged by FDA).

[20] 21 U.S.C.356b(a) and 21 CFR 314.81(b)(2)(vii) and 601.70(b).

[21] See the FDA's *Regulatory Procedures Manual* available at https://www.fda.gov/iceci/compliancemanuals/regulatoryproceduresmanual/default.htm.

[22] See section 505(o)(2)(A) of the FD&C Act for a definition of the term *responsible person*.

301(k) of the FD&C Act to do any act with respect to a drug, if such act is done while the drug is held for sale after shipment in interstate commerce and results in the drug being misbranded.

- Civil monetary penalties, pursuant to section 303(f)(4)(A) of the FD&C Act (21 U.S.C. 333(f)(4)(A)). Under section 303(f)(4)(A) of the FD&C Act, a responsible person who violates postmarketing study or clinical trial requirements of section 505(o) of the FD&C Act shall be subject to a civil monetary penalty of —

  — Not more than $250,000 per violation, and not to exceed $1,000,000 for all such violations adjudicated in a single proceeding; or

  — In the case of a violation that continues after FDA provides written notice to the responsible person, the responsible person shall be subject to a civil monetary penalty of $250,000 for the first 30-day period (or any portion thereof) that the responsible person continues to be in violation, and such amount shall double for every 30-day period thereafter that the violation continues, not to exceed $1,000,000 for any 30-day period, and not to exceed $10,000,000 for all such violations adjudicated in a single proceeding.

In determining the amount of a civil penalty, FDA will consider whether the responsible person is making efforts to correct the violation (see section 303(f)(4)(B) of the FD&C Act).

In general, warning letters for violations of section 505(o)(3) will be posted on FDA's website; untitled letters may also be posted.[23] FDA is not obligated to provide prior notice (e.g., warning letters) before taking enforcement action.

[23] See the FDA Warning Letters and Notice of Violation Letters to Pharmaceutical Companies web page available at https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/EnforcementActivitiesbyFDA/WarningLettersandNoticeofViolationLetterstoPharmaceuticalCcompanies/ucm594437.htm#OSI.