Field Alert Report Submission

Questions and Answers Guidance for Industry

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 2021
Pharmaceutical Quality/CMC

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TABLE OF CONTENTS

Contains Nonbinding Recommendations

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This guidance represents 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 office responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance provides FDA's current thinking regarding the requirements for submission of field alert reports (FARs) by applicants of new drug applications (NDAs) and abbreviated new drug applications (ANDAs) and outlines FDA's recommendations for FAR submissions to help improve their consistency and relevancy. The guidance also addresses certain frequently asked questions.

The contents of this document do not have the force and effect of law and are not meant to bind the public in any way, unless specifically incorporated into a contract. This document is intended only to provide clarity to the public regarding existing requirements under the law. FDA guidance documents, including this guidance, 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.

II. BACKGROUND

The FAR regulations found in 21 CFR 314.81(b)(1) establish an early warning system to help FDA fulfill its responsibility to protect patient health. Under these regulations, NDA and ANDA applicants must submit certain information to FDA about distributed drug products.[2] Specifically, the regulations state that an NDA or ANDA applicant must submit a FAR to FDA within 3 working days of receiving the following kinds of information for distributed drug product(s):

[1] This guidance has been prepared by the Center for Drug Evaluation and Research in cooperation with the Center for Biologics Evaluation and Research and the Office of Regulatory Affairs at the Food and Drug Administration.

[2] For purposes of this guidance, *applicant* has the meaning set forth in 21 CFR 314.3. Under § 314.98(b), each ANDA applicant must make the reports required under § 314.81.

> (i) Information concerning any incident that causes the drug product or its labeling to be mistaken for, or applied to, another article.
>
> (ii) Information concerning any bacteriological contamination, or any significant chemical, physical, or other change or deterioration in the distributed drug product, or any failure of one or more distributed batches of the drug product to meet the specification established for it in the application.[3]

This requirement applies to any product approved under an NDA or ANDA, including drug-device combination products,[4] positron emission tomography (PET) drugs,[5] and designated medical gases.[6]

In 2017, FDA introduced Form FDA 3331a, NDA/ANDA Field Alert, which helped move FDA away from manual data entry to an automated system of receiving FARs. Applicants holding NDAs or ANDAs regulated by the Center for Drug Evaluation and Research (CDER) or the Center for Biologics Evaluation and Research (CBER) may use Form FDA 3331a, which is available on FDA's Field Alert Reports website,[7] to submit FARs.

III. QUESTIONS AND ANSWERS

This section outlines your responsibilities as an NDA or ANDA applicant regarding FAR submissions and makes recommendations about providing information to FDA about root cause investigations, corrective actions, and other actions you take in response to a FAR.

1. What is a FAR and what triggers its submission?

a. What is a FAR?

FARs are part of an early warning system to protect patient health. You must submit a FAR for distributed drug products and articles to FDA if you receive information of the following kinds (21 CFR 314.81(b)(1)):

- Information concerning any incident that causes a drug product or its labeling to be mistaken for, or applied to, another article.

[3] This includes contamination by bacteria, yeast, mold, virus, or other microorganisms.

[4] See 21 CFR part 4, subpart B. FAR requirements also apply to distributed combination products containing a drug constituent part that are not approved under an NDA or ANDA. For additional information about FARs for these combination products, see guidance for industry and FDA staff *Postmarketing Safety Reporting for Combination Products* (July 2019). We update guidances periodically. 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.

[5] See guidance for industry *FDA Oversight of PET Drug Products: Questions and Answers* (December 2012).

[6] See section 576(a)(3) of the Federal Food, Drug, and Cosmetic Act.

[7] See https://www.fda.gov/drugs/surveillance/field-alert-reports.

- Information concerning any bacteriological contamination, or any significant chemical, physical, or other change or deterioration in the distributed drug product, or any failure of one or more distributed batches of the drug product to meet the specification established for it in the application.[8]

You should submit a FAR using Form FDA 3331a (see question 4a). In that form, and in this guidance, the term *problem* refers to the incident[9] or possible/actual quality issue[10] that is the subject of the FAR.

b. What are initial, follow-up, and final FARs?

This guidance uses the terms *initial*, *follow-up*, and *final* FARs, consistent with the language in Form FDA 3331a.

- *Initial FAR* refers to the FAR that you submit to comply with the requirements of § 314.81(b)(1), and it is the first time you have submitted a FAR about a specific problem as described in question 1a.

- *Follow-up FAR* refers to subsequent FARs you submit to provide additional information about the problem identified in the initial FAR. Examples of additional information include significant findings of the ongoing investigation; additional facilities or lots identified within scope; and sample analyses, laboratory test results, or potential root causes identified.

- *Final FAR* refers to the FAR you submit to close out the initial FAR identifying the root cause and describing corrective actions taken or to be taken.

Although follow-up and final FARs are not required, they are recommended. For more information on follow-up and final FARs, see III.6 in this guidance.

c. What is considered a significant chemical, physical, or other change or deterioration in the distributed product?

To determine whether a chemical, physical, or other change or deterioration in the distributed drug product is significant, you should evaluate the potential impact of the change or deterioration on the drug product's quality (such as identity, strength, purity, and stability) or efficacy and how that change or deterioration could impact an individual using the product. Any such assessment should be based on factors specific to your distributed product. These factors could include intended use, route of administration, dosage, length of treatment, and patient

[8] See footnote 3.

[9] See § 314.81(b)(1)(i).

[10] See § 314.81(b)(1)(ii).

population. Possible changes or deterioration in distributed product include contamination by bacteria, yeast, mold, virus, or other microorganisms.

You should also clearly document an investigation conducted according to 21 CFR 211.192, 211.198, 212.71, or 212.100, including the determination of whether a problem resulted in a significant chemical, physical, or other change or deterioration, along with the rationale (including factors considered) for the determination. If this determination is preliminary in the initial FAR, you should update the investigation in a follow-up or final FAR. (See question 1d for information about consumer complaints.)

d. Does every consumer or other customer complaint warrant submission of a FAR?

No, not every consumer or other customer complaint warrants submission of a FAR. Such complaints should be evaluated within 3 working days to determine if the information provided in the complaint meets the criteria outlined in § 314.81(b)(1). You must submit a FAR within that time frame if you determine that the information identified in the complaint meets the criteria for a FAR. See §§ 211.198 and 212.71 for more information on handling complaints.

e. Do I have to submit a FAR for problems related to packaging or components used in the manufacture of the distributed product?

If you receive information about packaging or components (e.g., active and inactive ingredients, processing aids) that meets the criteria set forth in § 314.81(b)(1), you must submit a FAR within 3 working days of your receipt of that information. For example, a FAR must be submitted if (i) you receive information that a stopper used for a vial could result in contamination of a distributed batch, or (ii) a component lot used in a distributed batch is later discovered to be failing a specification (unless you can scientifically determine that the failure does not impact the distributed batch within 3 working days of that discovery).

f. If the product approved under an NDA/ANDA is only distributed outside the United States, am I still subject to the FAR requirements?

Yes. Any drug product marketed under an approved NDA or ANDA, whether distributed domestically or abroad, is subject to FAR requirements.[11] Products that are not marketed under an NDA or ANDA (e.g., products that are only marketed abroad pursuant to a foreign approval, with non-U.S. labeling) are not subject to FAR requirements. However, a manufacturing problem with such a product may still lead to a FAR if the problem is also relevant to a product marketed under an NDA or ANDA. This may occur, for example, if the issue affects materials used to produce both products or if they are made on the same line.

[11] See § 314.81(b)(1).

g. If a product has not been distributed and an out-of-specification (OOS) result is discovered, is a FAR still required?

No. A FAR is only required for distributed drug products. However, if you discover an OOS result and your investigation indicates a failure of one or more distributed batches of the drug product to meet the specification established in the application, or other kinds of information as specified in § 314.81(b)(1) that relates to a distributed drug product, then you must submit a FAR.[12]

h. If an OOS result for a distributed drug product is discovered during stability testing, but the result is invalidated within 3 working days, do I need to submit a FAR?

No. OOS results for a distributed drug product that are scientifically invalidated (e.g., an analytical laboratory error is confirmed) within 3 working days do not require a FAR. If an OOS result is not scientifically invalidated, you must submit a FAR within 3 working days of your initial receipt of the OOS information.

i. Do aseptic process simulation (media fill) failures for a distributed drug product require a FAR?

A media fill failure indicates a potential problem related to sterility assurance that requires an investigation, including assessment of the impact on distributed drug products produced since the last successful media fill.[13] During that investigation, if you discover information about a distributed drug product that meets the criteria set forth in § 314.81(b)(1), you must submit a FAR within 3 working days.

j. If the root cause of a problem related to a distributed drug product is identified and corrected within 3 working days, should I still submit a FAR?

Yes, if you receive information as outlined in § 314.81(b)(1), you must submit a FAR within 3 working days regardless of whether an investigation identifies a root cause or leads to a corrective action. The report should include detailed information regarding the identified root cause and completed or ongoing corrective actions.

k. Is a FAR required if a recall is initiated?

You must submit a FAR if the information leading to the recall meets the criteria under § 314.81(b)(1). You should also submit a recall notification to FDA through your local recall coordinator (https://www.fda.gov/safety/industry-guidance-recalls/ora-recall-coordinators). If the recall is initiated after an initial FAR is submitted, we encourage you to submit a follow-up or

[12] See also guidance for industry *Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production* (October 2006).

[13] See §§ 211.192 and 212.50(b).

final FAR at the time of the recall notification.[14] A recall notification is not a substitute for a required FAR submission.

2. Who is responsible for submitting the FAR?

As the NDA/ANDA applicant, you must submit the FAR.[15] If you have a contractual agreement with another person or entity to perform manufacturing, holding, packaging, labeling, or distribution activities or services for your products, you still are responsible for submitting FARs within 3 working days. Your agreement with contracted entities should establish a procedure that those entities follow for notifying you of reportable information in a timely manner to ensure that you submit the FAR within 3 working days.[16]

3. When should I submit a FAR?

a. What is the required time frame for submitting a FAR?

You must submit a FAR within 3 working days of receipt of the information described in § 314.81(b)(1). We consider *working days* to be any day from Monday through Friday, excluding U.S. Federal holidays. For example, if information meeting the criteria requiring a FAR is identified on Friday (day 0), then day 1 begins on the first working day after the information is identified (Monday), and you must submit the FAR by close of business on Wednesday (day 3). This time frame applies regardless of where the information meeting the criteria requiring a FAR is identified. For example, the day a contract lab learns of a sterility failure is day 0, and you must submit the FAR by close of business on day 3.

b. What will happen if I do not submit a FAR within the 3-day time frame?

If you fail to submit a required FAR within this time frame, you would—at a minimum—be in violation of § 314.81(b)(1). You would also be in violation of section 505(k) of the Federal Food, Drug, and Cosmetic Act (FD&C Act).[17] Violating section 505(k) is a prohibited act under section 301(e) of the FD&C Act.[18] You must still submit a required FAR even if you fail to do so within the time frame of the regulation. We may include any failure to submit a FAR as an observation on Form FDA 483, Inspectional Observations. An FDA finding that you have failed to submit a FAR, as required, may result in a regulatory action, whether or not the finding was cited on Form FDA 483.

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[14] See 21 CFR part 7; FDA, 2016, Chapter 7: Recall Activities, Investigations Operations Manual, https://www.fda.gov/media/75263/download; and guidance for industry *Product Recalls, Including Removals and Corrections* (March 2020).

[15] See §§ 314.81(b) and 314.98(b).

[16] See guidance for industry *Contract Manufacturing Arrangements for Drugs: Quality Agreements* (November 2016).

[17] 21 U.S.C. 355(k).

[18] 21 U.S.C. 331(e).

4. How do I submit a FAR?

a. Is a form available to submit FARs?

Yes. We recommend that you use Form FDA 3331a to submit your FARs electronically. Submitting electronically will expedite FDA's review process and fulfill your obligation to submit the FAR to the relevant district office. We will, however, accept other types of submissions as described in § 314.81(b)(1).

Form FDA 3331a and its instructions are available on the FAR website at https://www.fda.gov/drugs/surveillance/field-alert-reports.

b. Is it necessary to submit two copies of a FAR if the FAR has been submitted electronically?

No. Electronic submission of Form FDA 3331a as outlined in the Form FDA 3331a instructions meets FAR requirements under § 314.81(b)(1).

c. Does submission of FDA Form 3331a satisfy the written follow-up requirement for FARs submitted initially by telephone?

Yes, using Form FDA 3331a as instructed will satisfy the written follow-up requirement for FARs initially submitted by telephone or other rapid means as set forth in § 314.81(b)(1). Once you use Form FDA 3331a to submit your FAR electronically, the information you entered will be available to CDER or CBER and FDA district (field) offices.

d. How should I report a problem that affects drug products covered by multiple applications?

You must submit a separate initial FAR for each application that is affected by the problem, regardless of whether the problem occurs in one facility or different facilities.[19] For example, if multiple NDAs or ANDAs are involved, submit one Form FDA 3331a for each application.

If you conduct a single comprehensive investigation into the problem after submitting the initial FARs, you can then submit one follow-up and/or final FAR that references all of the affected products, the NDA/ANDA number(s), and the date(s) the problem was identified.

e. What if I don't know the information asked for on Form FDA 3331a at the time of submission?

In an initial FAR, provide whatever information you have that is related to the problem within 3 working days of receipt of the information described in § 314.81(b)(1). Please be sure to report the NDA/ANDA number, the drug product generic name and trade/brand name (if any), the product quality issue, and your contact information. Providing as much information as you can

[19] See § 314.81(a).

about the known or possible causes of the problem being reported helps us evaluate its scope and potential impact and can help guide you to more efficient and prompt corrective actions.

When you learn more about the problem reported in the initial FAR, we recommend that you submit the new information in a follow-up or final FAR (see III.6).

f. Form FDA 3331a asks for the "date when notified about problem(s) or when problem(s) first became known to application holder." Is this the date when the information was confirmed as an actual problem?

No, it is the date you received information of the kinds outlined in § 314.81(b)(1). Follow-up and final FARs should contain the same initial date.

5. Where do I submit a FAR?

When you use the automated features of Form FDA 3331a, your FAR will be submitted simultaneously to CDER and to the FDA district office you select on page ii of the form. CDER will forward FARs to CBER, as appropriate. Form FDA 3331a provides contact information (e.g., email and postal addresses) for all district offices. For specific information about which district office to select on page ii of the form, see the questions and answers below.

a. If the problem occurs at a domestic facility in the United States, where do I indicate that facility's information on the FAR and where should I submit the FAR?

You should list the facility information in Form FDA 3331a's box 1—"Firm Name and Address Where Problem Occurred"—and select the FDA district office for that facility's location on page ii of the form. We recommend that you also cc: the district office where your headquarters is located (or U.S. agent, for foreign firms) if different from the FDA district office you selected on the form.

b. If the problem occurs at a foreign facility, where do I indicate that facility's information on the FAR and where should I submit the FAR?

You should list the foreign facility information in Form FDA 3331a's box 1—"Firm Name and Address Where Problem Occurred"—and, on page ii, select the FDA district office where your firm's attorney, U.S. agent, or other authorized official resides or maintains a place of business in the United States.[20]

c. If multiple firms or locations are implicated in an investigation, which firm or location should I list on the FAR as the site where the problem occurred?

You should enter the name and address of the finished drug product manufacturer for the NDA or ANDA in Form FDA 3331a's box 1—"Firm Name and Address Where Problem Occurred." However, if the problem involves the active pharmaceutical ingredient (API) or other component

[20] See 21 CFR 207.40 and 314.50(a)(5).

type or container closure system, you should list the supplier's facility information in box 1 instead. If the problem involves a firm other than the finished drug product manufacturer, such as a labeling and packaging firm, you should list that firm's information in box 1. If any firm other than the finished drug product manufacturer is listed in box 1, you should include the name and address of the finished drug product manufacturer in box 14, "Remarks," as well as additional sites implicated but not already included in box 1.

d. If it is unclear where the problem occurred, which location should I list on the FAR and where should I submit the FAR?

You should list the site where, to the best of your knowledge, the problem most likely occurred (see question 5c) in Form FDA 3331a's box 1—"Firm Name and Address Where Problem Occurred"—and, on page ii, select the FDA district office for that location. For example, if your prescription product is found to have one or more bottles containing the wrong tablet at the time the FAR is submitted, it could be unclear if the problem occurred at the tableting facility, during distribution in bulk containers to a final packager, or during final packaging, subsequent shipping and handling, or dispensing at the pharmacy. We recommend that you cc: the FDA district office where your headquarters is located (or U.S. agent, for foreign firms) if different from the district office for the location where the problem most likely occurred. List additional sites implicated in box 14, "Remarks."

If during the course of an investigation you wish to change the information initially provided or you have determined where the problem occurred, you should update the establishment name, address, and/or facility establishment identifier (FEI) number or the data universal numbering system (DUNS) number of the firm where the problem occurred in a follow-up FAR. If a new district office is the receiving district for your follow-up FAR, please also cc: the original district office that received the initial FAR.

6. Should I submit a follow-up or final FAR?

Although follow-up and final FARs are not required under § 314.81(b)(1), we recommend that you submit these additional voluntary reports, whenever warranted.[21] We use the information in these reports to assess the problem, risk to public health, and status and adequacy of your corrective action, or your determination that there was no actual defect as initially suspected. The information also helps us determine the need for an inspection or other surveillance activities and may prove helpful in addressing problems associated with component and container closure suppliers whose materials may be used by other drug product manufacturers.

a. When should I submit a follow-up FAR?

Though not required, we encourage you to submit follow-up FARs when (1) there are significant findings during the investigation of the problem identified in the initial FAR (e.g., additional lots impacted, different locations identified) or (2) you learn that information submitted in a previous FAR is incorrect.

[21] For a description of follow-up and final FARs, see question 1b.

b. During my investigation, if I discover that additional lots of the same drug product have the same issues as those identified in the initial FAR, should I submit a new FAR?

We recommend that you submit a follow-up FAR to identify the additional lots. In the follow-up FAR, you should reference the discovery date from the initial FAR, update FDA on the progress of the investigation, identify corrective actions that you have taken as well as those you intend to take, and provide the anticipated date for closing out the investigation in Form FDA 3331a's box 14 "Remarks."

c. If I receive an additional complaint while there is a FAR for the same problem still being investigated, should I submit a follow-up FAR?

If all of the following are true, you should not submit a follow-up FAR:

- The problem is the same as that identified in the initial FAR.
- The drug product is covered under the same NDA/ANDA as originally reported.
- The drug product is part of the same batch as originally reported.

When your root cause investigation for a FAR is ongoing (i.e., one for which no final FAR has been submitted), we recommend that you provide a cumulative list of related complaints in your final FAR rather than submitting a FAR for every complaint received.

d. When should I submit the final FAR?

We recommend submitting final FARs promptly to inform FDA when you identify the root cause, take corrective action, or close the investigation.