Field Alert Report Submission
Questions and Answers Guidance for Industry

DRAFT GUIDANCE

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For questions regarding this draft document, contact (CDER) Mamta Gautam-Basak 301-796-0712; (CBER) Office of Communication, Outreach and Development, 800-835-4709 or 240-402-8010; or (ORA) Rachel Harrington 410-779-5441.

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)
Office of Regulatory Affairs (ORA)

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Pharmaceutical Quality/Manufacturing Standards (CGMP)

Field Alert Report Submission

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Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993-0002
Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353
Email: druginfo@fda.hhs.gov
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Office of Communication, Outreach and Development
Center for Biologics Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 71, Room 3128
Silver Spring, MD 20993-0002
Phone: 800-835-4709 or 240-402-8010
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TABLE OF CONTENTS

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This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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 the agency'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 increase their consistency and relevancy. The guidance also addresses certain frequently asked questions.

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.

II. BACKGROUND

The FAR regulations found in 21 CFR 314.81(b)(1) and 314.98(b) establish an early warning system to help protect patient health. Under these regulations, NDA and ANDA applicants must submit certain information to FDA about distributed drug products regulated by the Center for Drug Evaluation and Research (CDER) or the Center for Biologics Evaluation and Research (CBER). Specifically, an NDA or ANDA applicant[2] 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[3] 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.

On May 2, 2013, FDA issued a *Federal Register* notice to notify the pharmaceutical industry about a voluntary pilot project using extensible markup language (XML) functionality to automate Form FDA 3331, NDA-Field Alert Report. The pilot, a collaborative effort between CDER and the Office of Regulatory Affairs (ORA), was the first step in moving FDA away from manual data entry to a more automated system of receiving FARs. It also allowed both CDER and ORA to receive FAR information simultaneously. All firms were encouraged to participate.

In June 2017, the pilot project was completed and a new version of the automated form—Form FDA 3331a, NDA/ANDA Field Alert—which incorporates feedback from pilot project participants, was approved by the Office of Management and Budget (OMB). Form FDA 3331a is available on FDA's Field Alert Reports website.[4] Although CBER did not participate in the pilot program, applicants holding NDAs or ANDAs regulated by CBER may also use the new form.

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 any 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. Per § 314.81(b)(1), you must submit a FAR for distributed drug products and articles to FDA if you receive information of the following kinds:

[3] FDA has interpreted the term *bacteriological* used in § 314.81(b)(1)(ii) to mean *microbiological*, which includes any kind of microbial contamination, such as bacteria, yeast, fungus, or virus. The contamination of distributed drug product by yeast, fungus, or virus would also be reportable as a *change or deterioration in the distributed drug product*, or as a *failure of one or more distributed batches of the drug product to meet the specification established for it in the application*.

[4] See https://www.fda.gov/drugs/guidancecomplianceregulatoryinformation/surveillance/ucm529729.htm.

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

- 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.

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[5] or possible/actual quality issue[6] 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 any 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 any 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.

[5] See § 314.81(b)(1)(i).

[6] See § 314.81(b)(1)(ii).

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 identity, strength, purity, stability, and 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 population.

You should also clearly document an investigation conducted according to 21 CFR 211.192 (production record review) or 211.198 (complaint files), 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. (See, e.g., question 1d for information about consumer complaints.)

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

No. Every consumer complaint 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.

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

If you receive information about packaging or components 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, if you receive information that a stopper used for a vial could result in contamination of a distributed batch, the information must be submitted in a FAR.

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.[7]

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[8] for example, indicates a failure of one or more distributed batches

[7] See § 314.81(b)(1).

[8] See § 211.192.

of the drug product to meet the specification established in the application, or other kinds of information as specified in § 314.81(b)(1), then you must submit a FAR.[9]

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 validation 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.[10] As such, you must submit a FAR for any distributed drug product within the scope of the media fill failure investigation within 3 working days of receiving information about such a failure if the information meets the criteria set forth in § 314.81(b)(1).

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 any completed or ongoing corrective action.

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

If the recall is for an NDA/ANDA product and the information leading to the recall meets the criteria under § 314.81(b)(1), you must submit a FAR. You should also submit a recall notification to FDA through your local recall coordinator (http://www.fda.gov/Safety/Recalls/IndustryGuidance/ucm129334.htm). If the recall is initiated after an initial FAR is submitted, we encourage you to submit a follow-up or final FAR at the time of the recall notification.[11]

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[9] See also guidance for industry *Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production.* We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

[10] See § 211.192.

[11] See 21 CFR part 7; FDA, 2016, Chapter 7: Recall Activities, Investigations Operations Manual; and guidance for industry *Product Recalls, Including Removals and Corrections.*

2. Who is responsible for submitting the FAR?

As the NDA/ANDA applicant, you must submit the FAR.[12] 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 hold ultimate responsibility for reporting FARs. You should establish, maintain, and follow a procedure for receiving and responding to any reportable information from contracted entities concerning your products.[13]

3. When should I submit a FAR?

a. What is the required time frame for the submission of 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 any 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).[14] Violating section 505(k) is a prohibited act under section 301(e) of the FD&C Act.[15] We may include this as an observation on Form FDA 483, Inspectional Observations. Any 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 a Form FDA 483.

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).

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[12] See §§ 314.81(b) and 314.98(b).

[13] See guidance for industry *Contract Manufacturing Arrangements for Drugs: Quality Agreements.*

[14] 21 U.S.C. 355(k).

[15] 21 U.S.C. 331(e).

Form FDA 3331a and its instructions are available on the FAR website at https://www.fda.gov/drugs/guidancecomplianceregulatoryinformation/surveillance/ucm529729.htm.

b. Is it necessary to submit a paper copy 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 the FDA district office responsible for the facility involved.

d. Can FARs associated with multiple NDAs/ANDAs be submitted on one form?

No. If multiple NDAs or ANDAs are involved, submit one Form FDA 3331a for each NDA or ANDA. See question 4e for additional information on submitting FARs for a facility-wide problem that affects drug products covered by multiple applications or application types.

e. How should I report a facility-wide problem that affects drug products covered by multiple applications or application types?

You must submit a separate initial FAR for each application (NDA or ANDA) that is affected by the problem.[16] If you conduct a single comprehensive investigation into the problem at a facility and you submit a follow-up or final FAR, you can submit one follow-up and/or final FAR that references all of the affected products, including the NDA/ANDA number(s) and the date(s) the problem was identified.

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

[16] See § 314.81(a).

g. 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). Any 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 responsible for that facility on page ii of the form. We recommend that you also cc: the district office where your headquarters is located 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.[17]

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 any raw material, 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

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

of the finished drug product manufacturer in box 14, "Remarks," as well as any 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?

If it is unclear where the problem occurred, 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 responsible for that location. For example, if your NDA/ANDA 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 or during distribution in bulk containers to the contract packager, packaging at a contract facility, subsequent shipping and handling, or dispensing at the pharmacy. We recommend that you cc: the FDA district office where your headquarters are located if different from the district office responsible for the location where the problem 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, when warranted, as soon as possible.[18] We use the information in these reports to assess the risk to public health and the adequacy of the firm's response.

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 any investigation for the same problem as that 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.

b. During the open 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?

If you choose to submit a follow-up FAR, you should submit a follow-up FAR that identifies the additional lots. In the follow-up FAR, you should reference the discovery date from the initial

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

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 consumer complaint while there is a FAR for the same problem still being investigated, should I submit a follow-up FAR?

No. A follow-up FAR should not be submitted if all of the following are true:

- 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 investigation into the root cause of the initial FAR is still ongoing.
- The drug product is part of the same lot as originally reported.

When there is an ongoing root cause investigation for a FAR (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 consumer 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. Investigations should be closed as soon as possible.