

October 22, 2001

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

5496 01 NOV 01 09:47

Re: Docket No. 01D- 0221
Comments on Draft "Guidance for Industry: Biological Product Deviation Reporting for Licensed Manufacturers of Biological Products Other Than Blood and Blood Components"

This letter respectfully provides the comments of the Orange County Regulatory Affairs Discussion Group (OCRA) on the above-cited CBER draft guidance document, in response to the Federal Register notice dated August 13, 2001.

OCRA Profile:

OCRA was organized in 1992 and incorporated in 1994. OCRA is chartered as a nonprofit educational group. OCRA's goals are to promote an atmosphere for open exchange of ideas and discussion for the Regulatory Affairs Professional from the Medical Device, Pharmaceutical, Biological, and Food and Cosmetic industries.

OCRA is truly a "grass roots" organization. Volunteers run our educational activities and OCRA does not have full time paid staff. We currently have over 500 active members primarily from the regulated industry in Orange County; California. OCRA does not have any corporate members. Small companies with less than 50 employees constitute a significant fraction of our members. Although we are Orange County based, our meetings consistently draw from all over the Western United States.

Comments:

Our specific comments on the draft guidance document, "Guidance for Industry: Biological Product Deviation Reporting for Licensed Manufacturers of Biological Products Other Than Blood and Blood Components," are provided on a copy of the document (enclosure). Suggested revisions are shown in red, with editorial comments in blue.

01D-0221

CZ



OCRA appreciates the opportunity to address these important issues. Please feel free to contact our organization at 949-222-9022 should you need further clarification of any of these comments.

Sincerely yours,

A handwritten signature in black ink that reads "Marcia S. Yaross". The signature is fluid and cursive, with a long, sweeping tail on the final letter.

Marcia S. Yaross, Ph.D.
President

Enclosure

SUGGESTED REVISIONS BY OCRA ARE IN RED
[COMMENTS BY OCRA ARE PROVIDED IN BLUE]

Draft Guidance for Industry

Biological Product Deviation Reporting for Licensed Manufacturers of Biological Products Other than Blood and Blood Components

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This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted by the date provided in the *Federal Register* notice announcing the availability of the draft guidance. Submit comments to Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

Additional copies of this draft guidance document are available from the Office of Communication, Training and Manufacturers Assistance, (HFMA-40), 1401 Rockville Pike, Rockville, MD 20852-1448, or by calling 1-800-835-4709 or 301-827-1800, or from the Internet at <http://www.fda.gov/cber/guidelines.htm>.

For questions regarding this document, contact Sharon O'Callaghan, at 301-827-6220 or by email at bp_deviations@cber.fda.gov.

**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research (CBER)
July 2001**

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Guidance for Industry

Draft - Not for Implementation

This guidance document represents the Agency's current thinking on biological product deviation reporting for licensed manufacturers of biological products other than blood and blood components. It does not create or confer any rights, privileges, or benefits on or for any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes and regulations.

I. INTRODUCTION

On November 7, 2000, the Food and Drug Administration (FDA) published a final rule to amend the regulation at 21 CFR 600.14 for reporting errors and accidents in manufacturing of biological products. The final rule

- eliminates the terms "error" and "accident" and focuses on biological product deviations, which include deviations and unexpected events
- establishes a reporting time frame of 45 days from the date the deviation or unexpected event was discovered established [Note from OCRA: There might be a fairly lengthy time between the discovery of a possible incident and the time when it is established as a deviation; A (real) example is an incident when the hydraulic seal of a pump was suspected to have leaked in the process fluid. The sealant was a silicon oil and it took up to a month to assay the process fluid and establish for certain that a leak did occur]
- limits reporting to deviations or unexpected events that are discovered after product distribution that may affect distributed products.
[Note from OCRA: This is ambiguous and we suggest rewording it to clearly reflect the requirement]

FDA published the rule for implementation within 180 days of the date of publication. This guidance document provides manufacturers of biological products other than blood and blood components, with the Agency's current thinking related to the biological product deviation reporting requirements. The FDA uses mandatory language, such as shall, must, and require, when referring to statutory or regulatory requirements. The FDA uses non-mandatory language, such as should, can, and recommend, when referring to guidance. It is the responsibility of the manufacturer to read, understand, and follow the regulations.

II. BACKGROUND

Previously, in accordance with 21 CFR 600.14, licensed manufacturers of biological products were required to promptly report to FDA errors and accidents

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in manufacturing that may affect the safety, purity, or potency of a product. In the Federal Register of September 23, 1997 (62 FR 49642), FDA published a proposed rule to amend the reporting requirements for manufacturers of biological products as described above. In response to some of the comments received, FDA is providing this guidance document to clarify the reporting requirements for manufacturers of biological products other than blood and blood components.

The amended regulation at 21 CFR 600.14 requires reporting of any event associated with the manufacturing, to include testing, processing, packing, labeling, or storage, or with the holding or distribution of a licensed biological product, in which the safety, purity, or potency of a distributed product may be affected. A manufacturer is required to report to the Center for Biologics Evaluation and Research (CBER), Office of Compliance and Biologics Quality (OCBQ) as soon as possible, but not to exceed 45 calendar days from the date of discovery of information reasonably suggesting a reportable event has occurred. To facilitate reporting, FDA has developed a standardized reporting format that may be submitted electronically or in paper form, by mail.

The amended regulation does not change any of the requirements in 21 CFR Part 211 or Part 820 for conducting investigations of manufacturing deviations or product deficiencies. Those regulations require a manufacturer to thoroughly evaluate and investigate as appropriate, unexplained discrepancies and failures to meet specifications, and to maintain complaint records, including records of investigations and follow-up. Procedures should include provisions for

- a timely investigation
 - a corrective action plan, both short term and long term, to prevent recurrence
 - procedures to gain control of unsuitable products in a timely manner
 - appropriate disposition of all affected products (in-date and expired)
- [Note from OCRA: there should be a time limitation to the requirement of this guideline which, as written, applies for perpetuity. Suggest this time boundary is the expiry date of the product.]

III. GUIDANCE

[As currently written, some of the “When” is embedded in the “What” section; this should be drawn out more clearly.]

A. WHO MUST REPORT? [Section 600.14(a)]

Under 21 CFR 600.14, the manufacturer who holds the biologics license and who had **control** over the product when the deviation or unexpected event (“event”) occurred must submit a biological product deviation report.

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[Note from OCRA: a better definition and an example of an “unexpected event” that would not be a reportable deviation ought to be provided in the document.]

“Control” is defined in section 600.3(ii) as having responsibility for maintaining the continued safety, purity, and potency of the product and for compliance with applicable product and establishment standards and compliance with current good manufacturing practices.

There may be firms, such as plasma fractionators, that collect Source Plasma or other blood components to be used as source material for further manufacture into a finished product. Deviations and unexpected events that occur during the manufacture of such source material should be reported under 21 CFR 606.171. Deviations and unexpected events that occur during the manufacture of a finished product that is licensed (e.g., Immune Globulin Intravenous, Human) must be reported under 21 CFR 600.14. A separate draft guidance document for reporting biological product deviations that occur in the manufacture of blood and blood components entitled “Biological Product Deviation Reporting for Blood and Plasma Establishments” is available from the Internet at <http://www.fda.gov/cber/guidelines.htm>.

Under 21 CFR 600.14, manufacturers of unlicensed source material (except for blood or blood components) are not required to report deviations and unexpected events that occur during manufacturing of the **unlicensed** source material. Deviations or unexpected events that occur in the manufacture of unlicensed material used as part of a clinical trial or IND application should be reported through the IND mechanism. The manufacturer of the finished licensed product must report deviations and unexpected events if the unlicensed source material is used in the manufacturing of the final product and the safety, purity, or potency of the final distributed product may be affected.

Sometimes, a manufacturer establishes a contract with another entity to perform some or all of the manufacture of a product. Some common manufacturing steps performed under contract include testing, filling, storage and distribution. If you contract out any manufacturing step, for the purposes of 21 CFR 600.14 and as described in this guidance document, that step is performed under your control. Under 21 CFR 600.14(a), you must establish a system for receiving information from that contract manufacturing facility on all deviations, complaints, and adverse events.

If you are a *Contract Manufacturer* (i.e., perform a step in manufacturing for another facility under contract), you must conduct such manufacturing in accordance with all applicable regulations, but you are not considered to

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have control over the product, for the purposes of submitting biological product deviation reports to FDA.

Examples

1. BIOLOGICAL PRODUCT DEVIATION

A vaccine manufacturer contracts with another establishment (contract filler) to perform the filling operation for the vaccine product. The filling operation was not performed in accordance with specifications provided by the manufacturer, which may affect the safety, purity, or potency of the product.

REPORTING

The contract filler must perform an investigation under 21 CFR 211.192 and 211.198. The contract filler should provide the manufacturer with the details of the deviation that occurred during the filling process, but is NOT required to report to FDA.

The manufacturer must establish a procedure for receiving information from the contract filler about deviations concerning the filling operation. The vaccine manufacturer must report a biological product deviation to FDA if it distributed the improperly filled product. The manufacturer should assure that the contract filler performed an adequate investigation.

2. BIOLOGICAL PRODUCT DEVIATION

A test kit manufacturer distributed an HBsAg test kit to a consignee. The consignee, a blood establishment, stored the product at an unacceptable temperature, which may affect the safety, purity, or potency of the product.

REPORTING

The test kit manufacturer is NOT required to report to FDA or perform an investigation, since the product was not in its control at the time the event occurred.

The consignee is required to perform an investigation under 21 CFR 606.100(c), 211.192 and 211.198, if they used the test kit for blood donor testing. The consignee is required to report a biological product deviation under 21 CFR 606.171, if the consignee distributed blood components that were tested using the improperly stored test kit. Additional guidance is provided in the draft document "Biological Product Deviation Reporting for Blood and Plasma Establishments."

3. BIOLOGICAL PRODUCT DEVIATION

A manufacturer received glass vials and stoppers from a vendor.

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The manufacturer determined that the vials and stoppers did not meet all required specifications, which may affect the safety, purity, or potency of the final product.

REPORTING

The manufacturer should notify the vendor and the vendor should investigate the deviation. The vendor is NOT required to report to FDA.

The manufacturer is NOT required to report to FDA unless it used the unsuitable vials and stoppers and distributed the final product.

4. BIOLOGICAL PRODUCT DEVIATION

A source plasma center collected and tested a unit, and shipped it to a fractionator. The plasma center then discovered that the testing was incorrectly performed for anti-HIV. When tested correctly, the unit actually tested repeatedly reactive for anti-HIV.

REPORTING

The plasma center must perform an investigation of the improper testing and release of the unit under 21 CFR 606.100(c), 211.192, and 211.198. The plasma center is required to report a biological product deviation to FDA under 21CFR 606.171. The plasma center should also notify the fractionator. Additional guidance is provided in the draft document "Biological Product Deviation Reporting for Blood and Plasma Establishments."

The fractionator is required to report a biological product deviation under 21 CFR 600.14, if it used the improperly tested plasma in the manufacture of a licensed biological product and distributed the final product, because the safety, purity, or potency of the final product may be affected.

B. WHAT DO I REPORT? [Section 600.14(b)]

You must report any event associated with the manufacturing, to include testing, processing, packing, labeling, or storage, or with the holding or distribution, of a licensed biological product that has been distributed, if that event meets all the following criteria:

1. Either;
 - i. Represents a deviation from current good manufacturing practices, applicable regulations, applicable standards, or established specifications that may affect the safety, purity, or potency of that product; or
 - ii. Represents an unexpected or unforeseeable event that may affect the safety, purity, or potency of that product; and

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2. Occurs in your facility or a facility under contract to you; and
3. Involves distributed biological product.

You must establish a procedure to determine when a biological product deviation or unexpected event [Note from OCRA: as this guidance associates deviation and unexpected event, it must be consistent throughout] must be reported to FDA. The procedure should include a process to assess whether or not an event is reportable. The decision to report should not be based on an investigation into whether the event affected the safety, purity, or potency, but whether the event had the potential to affect the safety, purity, or potency of a product. The procedure should not consist of a list of examples of reportable and non-reportable events alone. Examples may be included in the procedure for reference.

In general, a biological product deviation report is **not** required:

1. When no affected products are distributed, regardless of the deviation or unexpected event.
2. When it is determined prior to distribution that the safety, purity, or potency of a product is not affected
3. Simply to report that you were late in reporting the deviation or unexpected event to FDA.
4. When a deviation or unexpected event is detected and appropriately corrected, or the product is appropriately reprocessed or reworked by an FDA approved method, prior to distribution.
5. When there is a minor recordkeeping omission, such as omission of a date of review or batch records not independently reviewed by a second person, and the discrepancy or omission does not have the potential to affect the safety, purity, or potency of the product.

It is important to note that while the above examples would not be reportable under 21 CFR 600.14, the events may constitute deviations from the regulations, which will be assessed by FDA in the context of overall operations.

Biological Product Deviation Reporting Flow Chart

The following flow chart may be used to aid in determining if you are required to report an event to FDA.

[Note from OCRA: In the flow chart (red line attached)

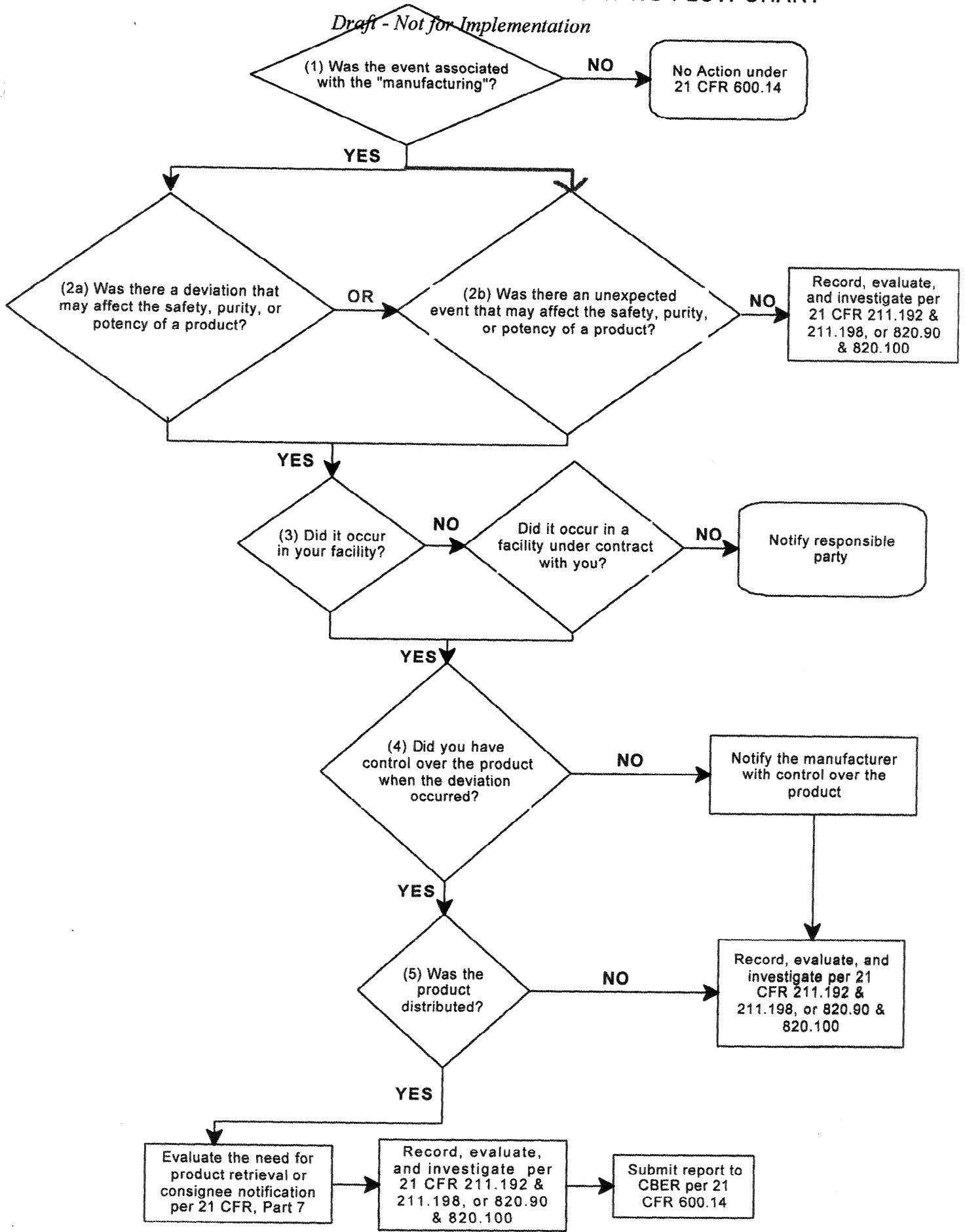
- i) First level: replace the “manufacturing” by “manufacturing activities”
- ii) Second level: replace “(2a) IF NOT (2b)” by “(2a) OR (2b)”

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BIOLOGICAL PRODUCT DEVIATION REPORTING FLOW CHART

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If...	And...	Then...
If the event was not associated with manufacturing	The deviation or unexpected event did not affect the safety, purity, or potency of the product	Take no action under 21 CFR 600.14
If the event was associated with manufacturing	The event did not occur at your facility or a facility under contract with you	Record, evaluate, and investigate per 21 CFR 211.192 & 211.198, or 820.90 & 820.100
If the event was associated with manufacturing and the deviation or unexpected event may affect the safety, purity, or potency of the product	You did not have control over the product when the deviation occurred	Notify responsible party
If the event was associated with manufacturing and the deviation or unexpected event may affect the safety, purity, or potency of the product and occurred at your facility or a facility under contract with you	The product was not distributed	Notify the manufacturer with control over the product and record, evaluate, and investigate per 21 CFR 211.192 & 211.198, or 820.90 & 820.100
If the event was associated with manufacturing and the deviation or unexpected event may affect the safety, purity, or potency of the product and occurred at your facility or a facility under contract with you, and you had control over the product when the deviation occurred		Record, evaluate, and investigate per 21 CFR 211.192 & 211.198, or 820.90 & 820.100
If the event was associated with manufacturing, and the deviation or unexpected event may affect the safety, purity, or potency of the product, and occurred at your facility or a facility under contract with you, and you had control over the product when the deviation occurred, and the product was distributed		Evaluate the need for product retrieval or consignee notification per 21 CFR Part 7, record, evaluate, and investigate per 21 CFR 211.192 & 211.198, or 820.90 & 820.100, and submit report to CBER per 21 CFR 600.14

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The following questions correspond to the flow chart:

(1) Was the event associated with the “manufacturing” as it is broadly described in the regulation?

In 21 CFR 600.14, manufacturing is described to include testing, processing, packing, labeling, or storage, and the holding or distribution, of a licensed biological product.

If the deviation or unexpected event was associated with manufacturing, you should determine whether the event may affect the safety, purity, or potency of a product. If it was not associated with the manufacturing, you are not required to report to FDA according to 21 CFR 600.14.

Deviations and unexpected events that occur after distribution of the product from the manufacturer are not reportable as a biological product deviation according to 21 CFR 600.14. These would include events that occur due to misuse or mishandling of the product by the user, such as administration errors.

In addition to biological product deviation reporting, manufacturers are also responsible for reporting adverse experiences and adverse events. Manufacturers of biological drug products are required to report adverse experiences in accordance with 21 CFR 600.80, and the Vaccine Adverse Event Reporting System (VAERS). Biological device manufacturers are subject to Medical Device Reporting in accordance with 21 CFR 803. If the adverse experience or adverse event occurs as a result of a deviation or unexpected event in manufacturing, the event should also be reported under 21 CFR 600.14.

(2a) Was there a deviation that may affect the safety, purity, or potency of a product?

A deviation that may affect the safety, purity, or potency of a product includes any change from the validated manufacturing process that would prevent a product from meeting all Current Good Manufacturing Practice (cGMP) requirements, applicable standards and established specifications. CGMP and applicable regulations are currently found in 21 CFR Parts 210, 211, 600, 610, 640, 660, 680, and 820. Established specifications refer to defined product or process parameters, including those that are part of your license application. Generally these are incorporated into standard operating procedures to help ensure the safety, purity and potency of products. They may describe the specifics of a product, such as the potency, or the specifics of a process, such as the mixing time.

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(2b) Was there an unexpected or unforeseeable event that may affect the safety, purity, or potency of a product?

An unexpected or unforeseeable event is one in which despite the fact that a manufacturer followed all required procedures, something occurred that may affect the safety, purity, or potency of a product. This may be due to information that the manufacturer did not have at the time of manufacturing. Examples of unexpected or unforeseeable events in which the safety, purity, or potency of the product may be affected include the following:

- i. After the product is distributed, the manufacturer is informed by a vendor of products used in the manufacturing process, such as reagents, equipment, or software, that the vendor's product did not meet all requirements or specifications, and the manufacturer's qualification process could not have identified the deficiency.
- ii. After the product is distributed, the manufacturer is informed by a vendor of products used in the manufacturing process, such as reagents, equipment, or software, that the vendor's product did not meet all requirements or specifications, and the manufacturer's qualification process could not have identified the deficiency.

[Note from OCRA: The guidance examples should cover the case of a deviation affecting an active ingredient, where said deviation might affect the quality, strength, etc., etc., of the final product in which the active ingredient was involved. This is not clear in the guidance.]

If an event occurred, but could not affect the safety, purity or potency of a product, it must be recorded, evaluated, and investigated in accordance with 21 CFR 211.192 and 211.198 for drug products and 21 CFR 820.90 and 820.100 for device products, but no biological product deviation report to FDA is required.

*If you discover a deviation or unexpected event **after** distribution of any affected product and the safety, purity, or potency of the product may have been affected at the time of distribution, you are required to report the event. You must report the event under 21 CFR 600.14 even if you determine, through investigation, that the safety, purity and potency of the product was not affected.*

For example, if you distributed a product that was not tested for all required parameters, you must report that to FDA, even if you subsequently tested the product and found it to be acceptable.

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*If you discover a deviation or unexpected event **prior** to distribution of any affected product and*

- *determine that the safety, purity, or potency of the product was not affected or*
- *reprocess the product in accordance with a procedure that is approved by CBER, or*
- *otherwise correct the problem (such as perform necessary testing if it is discovered that release testing was not performed)*

you do not need to report under 21 CFR 600.14.

For example, if you discovered a deviation in testing prior to the distribution of a product and you appropriately retested the product and found it to be acceptable, you are not required to report to FDA under 21 CFR 600.14.

(3) Did it occur at your facility or at your contract facility?

A report is required if the event occurs within your facility or a facility under contract to you, such as a testing laboratory or contract filler. You must report events that occur at the contractor and, therefore, you must establish, maintain, and follow a procedure for receiving information from the contract facility on all deviations, complaints, and adverse events concerning the affected product.

If you are a *contract manufacturer*, such as a testing laboratory or contract filler, and an event occurs within your facility, you should notify the manufacturer with control over the product. You are not responsible for reporting the event to FDA.

If you detect an event that occurred at another facility not under contract with you, you should contact that facility, which would be responsible for reporting to FDA, if appropriate. For example, if you receive licensed bulk material that was shipped under improper conditions you should notify the supplier. You are not required to report to FDA unless you use the unacceptable bulk material for manufacturing into a final product and distribute that product.

(4) Did you have control over the product when the deviation occurred?

You have control over the product if you have overall responsibility for

- maintaining the continued safety, purity, and potency of the product
- compliance with applicable product and establishment standards, and
- compliance with current good manufacturing practices

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You are responsible for reporting if you have control over the product and distributed the affected product.

You have control over the product if you contract with another entity to perform all or some of the manufacture of a product. Under 21 CFR 606.171(a), you must establish a system for receiving information from the contract manufacturing facility on all deviations, complaints and adverse events. The contract manufacturer is responsible for documenting, recording, evaluating, and investigating the event in accordance with 21 CFR 211.192 and 211.198 for drug products, or 820.90 and 820.100 for device products. The contract manufacturer is not responsible for reporting to FDA.

(5) Was the product distributed?

Distributed is defined in section 600.3(hh) as the biological product has left the control of the licensed manufacturer.

If the product was distributed, you should also assess the need for product retrieval or consignee notification in accordance with 21 CFR Part 7. The event must be recorded, evaluated, and investigated in accordance with 21 CFR 211.192 and 211.198 for drug products, or 820.90 and 820.100 for device products, regardless of whether or not the product was distributed.

A. WHEN DO I REPORT? [Section 600.14 (c)]

You must report a biological product deviation as soon as possible, but at a date not to exceed 45 calendar days from the date that you ~~acquire~~ ~~information reasonably suggesting~~ establish that a reportable event has occurred. You ~~acquire~~-establish such information when any employee of your facility, not just those involved in quality assurance or quality control, ~~learns~~-obtains data or reliable information about the event. [Note from OCRA: Deviations should be reported no later than 45 days after it has been established that a deviation or unexpected event did occur] As soon as you ~~acquire~~-reasonably establish ~~information~~-that a reportable event has occurred, you should make an assessment of whether the event had the potential to affect the safety, purity, and potency of products and determine the status of the products (whether they were distributed or need to be quarantined).

If you contract with a facility to perform a manufacturing step and a deviation or unexpected event occurs at the contractor, the time period for reporting will start when your contractor learns about the deviation or unexpected event.

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B. HOW DO I REPORT? [Sections 600.14 (d) and (e)]

You must use FDA Form-3486 to report biological product deviations. This report may be submitted electronically through CBER's web site at www.fda.gov/cber/biodev/biodev.htm, or by mail to:

Director, Office of Compliance and Biologics Quality (HFM-600)
Center for Biologics Evaluation and Research
1401 Rockville Pike, Suite 200N
Rockville, Maryland 20852-1448

If the event occurred at your contract manufacturer, you should include in the Biological Product Deviation Report details reported to you by the contract manufacturer regarding the event.

IV. EXAMPLES OF REPORTABLE AND NON-REPORTABLE EVENTS BY SYSTEM

FDA categorizes biological product deviations according to the system where the breakdown or failure occurred that resulted in the distribution of an unsuitable product. It is important for you to know where the failure occurred that allowed the product to continue through the process of manufacturing and distribution, so that you can take the appropriate follow-up action. An event may be the result of a failure within a variety of systems, depending on the circumstances.

- A deviation or unexpected event involving *incoming material specifications* is one that occurs during the process of receipt and acceptance of incoming materials (See Section IV. A.)
- A deviation or unexpected event in *process controls* occurs during the manufacturing process (See Section IV. B.).
- *Sampling and testing* deviations and unexpected events occur during the in-process and release testing process (See Section IV. C.).
- *Product labeling* deviations and unexpected events occur during the labeling process which includes identifying the information to include on the label, printing the label, and applying the label to the product (See Section IV. D.).
- A deviation or unexpected event involving *product specifications* means a product failed to meet one or more of its final product specifications, at product release or at anytime during the labeled dating period (See Section IV. E.).
- A deviation or unexpected event in *quality control and distribution* is one that occurs during the quality control or quality assurance approval process or during distribution of the final product (See Section IV. F.).

Retrieval and Consignee Notification

You must implement and follow procedures for the retrieval of products and

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consignee notification and maintain adequate records for such retrieval or notification. You are not required to file a biological product deviation report simply because you fail to follow your own internal procedures for retrieval or notification (e.g., you did not notify consignees within the time frame prescribed in your procedures). This type of deviation is not required to be reported because the safety, purity, or potency of the product was not affected by the failure to follow retrieval or notification procedures. However, you must file a report if the underlying reason for the retrieval or notification meets the reporting criteria found in Section III.B, What Do I Report. In that case, the report must describe the deviation or unexpected event that may have affected the safety, purity, or potency of the product and describe the failure to follow procedures.

The following examples of deviations and unexpected events are not all-inclusive and do not represent all variations that may occur. The examples include deviations from the regulations, standard operating procedures (SOPs), and established specifications. Not all of these examples will necessarily apply to you, but will depend on your manufacturing operations and procedures. All deviations and unexpected events must be investigated in accordance with 21 CFR 211.192 and 211.198 for drug products or 21 CFR 820.90 and 820.100 for device products, regardless of whether or not they are reportable.

A. INCOMING MATERIAL SPECIFICATIONS

Incoming materials include, but are not limited to, source material, raw material, reagents, containers and closures used in manufacturing. A deviation or unexpected event involving incoming material specifications is one that occurs when you receive, accept and manufacture licensed products from incoming materials that, either known or unknown to you, are defective, do not meet established specifications, or otherwise may affect the safety, purity, or potency of the licensed product.

A biological product deviation report **is required** when any of the following events occur, licensed products are manufactured using the material, and **distributed**:

- Containers or closures (e.g., stoppers) do not meet specifications or are found to be defective
- Source or raw material does not meet specifications or is otherwise found to be unsuitable
 - Contaminated with microorganisms or mold (if required to be sterile)
 - Chemical impurities exceed specifications
 - Contains precipitate (specification not met)
 - Testing deviation (required testing not performed or performed incorrectly)
 - Tested positive for viral marker (e.g., Source Plasma, recovered plasma)

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- Storage or shipment at incorrect temperature (e.g., lack of controlled shipment temperature for sensitive material)
- Reagent does not meet specification (e.g., used out of date reagents)

Incoming Material Specifications

DO NOT REPORT:

- Material does not meet specifications and is rejected or not used in manufacturing
- Source material (e.g., Source Plasma, recovered plasma) that is collected from donors who provide post donation information of high risk behavior and the source material tested negative for all viral markers

Note: FDA will already receive reports of post donation information concerning high risk behavior from blood establishments. Do report the receipt of other post donation information (example; donor is diagnosed with CJD or variant CJD) if deviation may affect the safety, purity or potency of the product.

B. PROCESS CONTROLS

A deviation or unexpected event in process controls occurs during the manufacturing process, which may affect the safety, purity, or potency of the product.

A biological product deviation report **is required** when any of the following events occur and products are **distributed**:

- Manufacturing or processing performed using incorrect parameters
 - incorrect temperature
 - filling procedures not performed according to specifications
 - aseptic processing procedures not performed according to specifications
- Bulk or intermediate product stored improperly
 - incorrect temperature
 - for excessive hold time
- Interruption of manufacturing process (e.g., due to a power outage)
- Sanitization procedures not performed or performed incorrectly
- Media fill failure (products potentially affected are those manufactured since last successful media fill)
- Environmental monitoring does not meet established specifications
- Equipment not operating within specifications
- Equipment failure

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- Bulk material does not meet specifications or is otherwise unsuitable
 - Contaminated with microorganisms or mold (if required to be sterile)
 - Chemical impurities exceed specification
 - Contains precipitate (specification not met)
- In-process specification not met

[Note from OCRA: Section B states that a deviation report is required when any of the events listed did occur and products are distributed. The issue is that several of these events represent deviations that may be properly investigated and resolved prior to distribution with a final resolution by QA that the lot may be released or that the release does not need to be questioned, and that the safety, purity, and potency of the product is not compromised. This section of this guidance would suggest that those deviations still ought to be reported as it does not include provisions for proper investigation and assessment. For example, “interruption of manufacturing process due to, for example, a power outage” may be properly investigated and found to be of no consequence if previous validation studies with simulated power outages were performed. The deviations falling within this category should not be reportable under this guidance.]

Likewise “environmental monitoring does not meet established specifications” is mentioned in this section of the guidance. Environment monitoring is performed against alert and action limits; proper corrective action(s) might have been taken to ensure that the deviation was of no consequence to the product and the deviation should not be reportable under this guidance.]

C. SAMPLING AND TESTING

Sampling and testing deviations and unexpected events include those that occur during the testing process. This includes testing that was not performed or was performed incorrectly. It includes situations where there is no record of testing and the safety, purity, or potency of the product may be affected.

A biological product deviation report **is required** when required testing was not performed, was performed incorrectly, or when there is no record of testing and products are **distributed**. Examples of testing where deviations may occur include

- Safety testing
- Purity testing
- Potency testing
- Sterility testing
- Identity testing
- Stability testing

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D. LABELING

Labeling deviations and unexpected events include those that occur during the labeling process. Labeling deviations include incorrect, missing or misleading information on any labeling pertaining to the product, including the unit label, the package insert, carton labels, and any other labeling accompanying the product, which may affect the safety, purity, or potency of the product.

A biological product deviation report **is required** when the any of the following events occur and products are **distributed**:

- Package insert is incorrect, not the current approved version, or not included with product
- Information missing or incorrect, such as product type, lot number, storage temperature, concentration or volume, administration route
- Product labeled with an extended expiration date, even if the product is expected to be used within the correct dating period
- Product missing expiration date

Labeling

DO NOT REPORT:

- Product labeled with a shortened expiration date, provided the date was not shortened because the product may not meet its specification through the entire approved dating period

E. PRODUCT SPECIFICATIONS

A deviation or unexpected event involving product specifications is one that occurs when the product does not meet its specifications, either at the time of distribution or at any time during the labeled shelf life of the product, and the safety, purity, or potency of the product may be affected. Product may have been inappropriately or incorrectly analyzed during release testing, or may have deteriorated over time. These events may be discovered during an audit, during investigation into a consumer complaint or during stability testing.

A biological product deviation report **is required** when any of the following events occur and products are **distributed**:

- Final product specifications are not met, such as
 - Potency
 - Moisture content
 - Preservative content
- Final product unsuitable
 - Contaminated with microorganisms or mold
 - Chemical impurities exceed specification
 - Contained precipitate (specification not met)

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3. Draft Guidance; Biological Product Deviation Reporting for Blood and Plasma Establishments

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- Stability testing failed during the labeled dating period

F. QUALITY CONTROL AND DISTRIBUTION

A deviation in quality control and distribution includes deviations or unexpected events in which

- Quality control or quality assurance procedures were not followed or not performed, and the safety, purity, or potency of the product may be affected
- A product was incorrectly distributed due to a failure in the distribution system and the safety, purity, or potency of the product may be affected

A biological product deviation report **is required** when any of the following events occur and products are **distributed**:

- Product distributed prior to completion of all required testing
- Product distributed prior to CBER approval of a PAS [Acronym to be clarified]
- Product distributed less than 30 days after submission of CBE [acronym to be clarified] supplement
- Product distributed prior to resolution of any discrepancy in manufacturing, that may affect the safety, purity, or potency of the product
- Product quality control deemed unacceptable
- Product released prior to validation of manufacturing process
- Outdated product
- Product shipped at incorrect temperature or with lack of assurance that controlled temperatures were maintained during shipment when controlled storage is required
- Product under quarantine or rejected was distributed

Quality Control and Distribution

DO NOT REPORT:

- Product shipped to the incorrect facility
- Discrepancy between the shipping document and the shipment, as long as the product is otherwise properly labeled
- Customer order filled incorrectly (wrong product, wrong amount), provided the product was labeled appropriately

V. REFERENCES

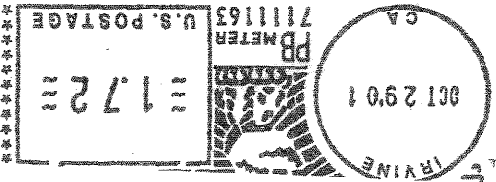
1. Biological Products; Reporting of Errors and Accidents in Manufacturing Proposed Rule (62 FR 49642, September 23, 1997).
2. Biological Products: Reporting of Biological Product Deviations in Manufacturing Final Rule (65 FR 66621, November 7, 2000)

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