

Expectations of Field Alert Report (FAR) and Biological Product Deviation Report (BPDR) Submissions

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An Update of Field Alert Reports and Biological Product Deviation Reports May 24, 2023

Learning Objectives



For Abbreviated and New Drug Application Field Alert Reports (FARs) and CDER Biological Product Deviation Reports (BPDRs, non-blood):

- Identify the type of information CDER expects in a submission.
- Understand key components of these reports .
- Understand the value of specific information about root cause investigations and Corrective Action and Preventative Action (CAPA).
- Understand the correlation between the MedDRA terms when identifying root cause investigations.



Identify the type of information CDER expects in FAR submissions

Identify the type of information FDA expects in a FAR submission

FDA

A/NDA Field Alert Report (FAR):

21 CFR 314.81(b)(1) provides the framework for NDA and ANDA applicant holders to provide

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

•*Reporting requirements* -The applicant shall submit information.....to the FDA district office that is responsible for the facility involved within 3 working days of receipt by the applicant. The information may be provided by telephone or other rapid communication means, with prompt written follow up."

NDA/ANDA Field Alert



Marketed drugs manufactured

DEPARTMENT OF HEAL TH AND HAMAN SERVICES Pool and Drug Administration NDA/ANDA FIELD ALERT Werefulniturer Control # Type of Report (Select al full apply in accordance with Sector 314 8/00(11) and (ii) of the New Drug Application Regulations (21 CFR 334) promugated under the Federal Food, Unig and Content: Art, as an enceded, the following information is herewith automated to Prevale and Admine When Problem Occurred The New Department of the Montent of the Sector 114 8/00(11) and (iii) of the New Drug Application Regulations (21 CFR 334) promugated under the Federal Food. Unig and Content: Art, as an enceded, the following information is herewith automated The New The New Due Sector 114 8/00(11) and (iii) of the New Drug Application Regulations (21 CFR 334) promugated under The New Due Sector 114 8/00(11) and (iii) of the New Drug Application Regulations (21 CFR 334) promugated under the Federal Food Insta and Content: Art, as an enceded, the following information is herewith automated The New Due Sector 114 8/00(11) and (iii) of the New Drug Application Regulations (21 CFR 334) promugated under the Federal Food Insta and Content: Art, as an enceded, the following information is herewith automated The New Due Sector 114 8/00(11) and (iii) of the New Drug Application Regulations (21 CFR 334) promugated under the Federal Food Insta and Content: Art, as an enceded, the following information is herewith automated The New Due Sector 114 8/00(11) and (110) and (Select one primary address by ma When filling out this form in Adobe • The selected address will be the To' is senail address will be the To' [] New York District (NYK-DO) 158-15 Liberty Ave. Jamaica, NY 11433 Tel: 718-340-7000 ORANYKFAR @Ida.hhs.gov	FDA/ORA FIELD ADDRESSE arking the box next to an address below. Reader: ally will be placed in the upper right area or addresse in the email generated by the s Denote Distinct (DC - DCV) 300 River Place, Suite 5900 Detroit, MI 48207-3179	S I form page 1, and ubmit button on the last form page. Dallas District (DAL-DO) 4040 North Central Expsyv.
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	Stoneham, MA 02180	Atlanta, GA 30309	250 Marquette Avenue, #600
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	Philadelphia, PA 19106	Nashville, TN 37217-2597	Lenexa, KS 66214-3340
	Tel: 215-597-4390	Tel: 251-344-8208, ext. 105	Tel: 913-752-2769
	ORAPHIFAR @fda.hhs.gov	ORANOLFAR@fda.hhs.gov	ORAKANFAR@fda.hhs.gov
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and the second	Baltimore District (BLT-DO)	Denver District (DEN-DO)	San Francisco District (SAN-DO)
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an analysis (and a	Baltimore, MD 21215	6th Avenue & Kipling Streets	Alameda, CA 94502-7070
	Tel: 410-779-5455	PO Box 25087	Tel: 510-337-6790
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	New Jersey District (NWJ-DO)	ORADENFAR@fda.hhs.gov	Seattle District (SEA-DO)
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		ORAFLAFAR@fda.hhs.gov	
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	-	ORASJNFAR@fda.hhs.gov	-
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1. Sales Producting	15th Floor		
	Chicago, IL 60661		
	Tel: 312-353-5863	YV YV	/IL Schama
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FAR Submissions of FDA Form 3331a



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Page 1 of 3

A/NDA applicant holders manufactures or distributes drugs internationally; and their product has a deviation, they are required to submit a FAR through:

<u>International FAR reporting</u> <u>requirements</u> - U.S. Office/Agent (21 CFR 314.50(a)(5)) is responsible for reporting to the FDA District Office where they are registered

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Submissions of A/NDA FAR

	DEPARTMENT OF HEA Pool and D NDA/ANDA	LTH AND HUMANI SERVICES up Administration FIELD ALERT	To, phase and Ad	Rests of District, per page 4 selections			
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Form FDA 3331a – Structured reporting format

- Manufacturer control number, should be the same number for ٠ each FAR initial, follow-up or final, without suffixes or prefixes.
- NDA or ANDA number ٠
- ٠ NDC Number – labeler code, product code; https://www.accessdata.fda.gov/scripts/cder/ndc/default.cfm
- Generic name; Brand name ٠
- Dosage strength and package size ٠
- Lot numbers and expiration dates, volume follow the format ٠ provided
- Number of complaints received for that batch ٠
- Date when notified ٠
- How the problem was discovered feeds into your root cause ٠ analysis

FAR Key Reporting Requirements

13. Reputed Gaality insue/Celeri (Provide the most specific quality insuedlebri		MedDRA product quality defect code
14. Describe Root Cause(s) of Problem(s)		
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FDA



MedDRA Coding for Product Quality

MedDRA Terminology for Coding



- Medical Dictionary for Regulatory Activities (MedDRA)
 - Standardized medical terminology developed by the International Council for Harmonisation (ICH) of Technical Requirements for Pharmaceuticals for Human Use
- Purpose: To facilitate sharing of regulatory information internationally for drugs, vaccines and combination products.
- MedDRA is a global terminology used by regulatory authorities and industry throughout the regulatory cycle pre-marketing to post-marketing for data entry, retrieval, evaluation, presentation.

MedDRA Terminology



FDA proposed a 27th System Organ Class (SOC) to MedDRA to incorporate Product Issue

- Terms based on Federal Food Drug and Cosmetic Act (FD&C)
- Current Good Manufacturing Practices
- 21 CFR 210, 211 ensures proper design, monitoring, and control of manufacturing processes and facilities.
- Guarantees that drugs will meet identity, strength, quality, and purity.



MedDRA Allows Intersect between Quality Defects and Adverse Events Data

CGMP Failures Product Quality Issues: FAR, BPDR



MedDRA and ICH



- MSSO (Maintenance and Support Services Organization): contracted by ICH with technical and financial oversight by the MedDRA Management Committee, to manage MedDRA versioning, subscriptions and training.
- ICH MedDRA Points to Consider (PtC) working group: developed and maintains guides for harmonized MedDRA coding and data retrieval.
 - Coding standard: ICH MedDRA® Term Selection PtC, already contains a section on Medication errors and separately Product quality issues
 - "Companion document" on coding of Product Quality Issues

MedDRA Hierarchy Levels and Quality

Issues



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The 27 SOC - Product Issues MedDRA version 26.0

FDA

- E-soc Product issues
 - 🗄 📅 Device issues
 - in the substant section in the section is the secti
 - Counterfeit, falsified and substandard products
 - HIT Manufacturing facilities and equipment issues
 - Hanufacturing issues NEC
 - HIT Manufacturing laboratory controls issues
 ■
 - manufacturing materials issues

 - Product contamination and sterility issues
 - Product distribution and storage issues
 - Product label issues
 - Froduct packaging issues
 - HIT Product physical issues
 - HIT Product quality issues NEC

HLT Manufacturing Laboratory Control Issues



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HLT Manufacturing Material Issues

- Manufacturing materials issues
 - Manufacturing material testing deviation
 - Im Manufacturing material testing deviation
 - E Manufacturing materials contamination
 - ur Manufacturing active pharmaceutical ingredient contamination
 - ur Manufacturing excipient contamination
 - ur Manufacturing inactive ingredient contamination
 - --- ur Manufacturing materials contamination
 - Im Manufacturing raw material contamination
 - E Manufacturing materials issue
 - ut Incoming material container closure out of specification
 - ut Incoming material container defective
 - ur Incoming material container out of specification
 - mut Manufacturing active pharmaceutical ingredient issue
 - ur Manufacturing component issue
 - -ur Manufacturing excipient issue
 - ur Manufacturing inactive ingredient issue
 - -ur Manufacturing material impurities
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 - -ur Manufacturing raw material issue
 - Product raw material issue

FDA

HLT Product Contamination and Sterility HLT Production Distribution & Storage Issues



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Expectations In Root Cause Investigations

Expectations of Root Cause Investigation



- Identify and provide a detailed description of the Failure Mode and Effects Analysis.
- Is the failure a process performance or product quality? How are the system's integrated?
- Is there a trend or signal seen across batches?
- What is the pharmaceutical quality management system's response?
- What is the risk to patients?
- ICH Q9 (R1) Quality Risk Management, May 2023

Corrective Action and Preventative Action (CAPA)

- A detailed plan of the proactive measures used to mitigate the risk is encouraged.
- What metrics are in place such as quantitative, analytical, microbial testing data to ensure that reoccurrence of failure are quickly detected?
- What is the communication plan of the Quality Management System to respond to and communicate failures?



Critical Quality Attributes is defined by ICH Q8 (R2) Pharmaceutical Development as physical, chemical, biological or microbiological properties or characteristics that should be within appropriate limit, or distribution to ensure the desired product quality."

Manufacturing defects may affect one or more of the drug quality attributes.

- Identity
- Strength
- Purity
- Quality/Performance



1) Identity tests

Drug substance and drug product fails to meet established performance specifications:

Manufacturing/formulation

- Starting Material, intermediates and final drug substance
- FT-NIR, optical rotation USP<781>, melting point, etc.



- o 2) Strength
 - Assay, USP or NDA/ANDA methodology should be specified; 90%-110%
 - Content Uniformity

o (USP <905>)

- Stability Timepoints
 - Modification to accelerated and Controlled Room Temp should be identified



- 3)Purity of drug product Quantitative data
 - Impurities (ICH Q3A/Q3B)
 - Degradation products (ICH Q3A/Q3B)
 - Residual solvents (ICH Q3C)
 - Chemical or Microbial Contamination Objectionable pathogen, sterility, PCR

Critical Attributes for Drug Quality

- 4) Quality/ Performance
 - Drug Substance
 - Particle sizes and shape within specifications, especially important for solubility
 - Drug product
 - Appropriate drug delivery system
 - o Suitable excipients
 - Consistent dissolution rate, .etc

FAR Case Study



- Pharmaceutical Company X manufactures an oncological drug called Fluorouracil Injection, USP lot 55-555 expiration date of Oct. 2024. This sterile liquid was manufactured in a Type I clear vial. At 3-month stability time point the HPLC assay value resulted in 85.0%.
- What type of root cause investigation should the company provide to FDA regarding this OOS result?
- Within 3 working days the company submitted an initial FAR to FDA.

Fluorouracil Injection Root Cause

- FDA
- The firm performed a retrospective review of their stability data at 0, 3 and 6 month time points.
- They reviewed 0 time: the results were 90.0% within specifications of 90.0% -110.0%. However by 3 months time pt. the product was OOS.
- What type of documentation, data and testing plan should the firm perform?
 - Impurity profile, degradation testing?
 - What knowledge of the Fluorouracil active did they exclude?
- (Hint) Is the packaging and container closure system a factor?



Identify the Type of Information CDER Expects in BPDR Submissions

Biological Product Deviation Reports (BPDRs)



- A manufacturer, who holds a biological product license and has control over the product when a deviation has occurred, must report it to CDER, as required by 21 CFR 600.14 ("Reporting of biological product deviations by licensed manufacturers").
- The responsible firm must report as soon as possible, but not to exceed
 45 calendar days from the date of discovery any information that may affect the product's safety, purity or potency including:
 - Manufacturing, including testing
 - Processing
 - Packaging
 - Labeling
 - Storage/ Holding
 - Distribution

CBER-Regulated Biologics

What does CBER regulate?

- Biological products, including blood and blood products, blood derivatives, vaccines, allergenics, gene therapies, cellular therapies, and xenotransplantation.
- Human cells and tissue products (HCT/Ps) that are intended for implantation, transplantation, infusion, or transfer into a human recipient. This may include bone, ligament, skin, dura mater, heart valve, cornea, hematopoietic stem/progenitor cells derived from peripheral and cord blood, manipulated autologous chondrocytes, epithelial cells on a synthetic matrix, and semen or other reproductive tissue.
- Medical devices involved in the collection, processing, testing, screening, manufacture and administration of blood, blood components, and human tissue and cellular products.
- HIV test kits used to screen donor blood, blood components and tissue and cellular products (HCT/Ps), and products used to diagnose, treat, and monitor persons with HIV and AIDS.
- Certain drug products, including blood bags with anti-coagulant, and plasma volume expander.

CDER-Regulated Biologics



Biologics transferred to CDER from CBER on June 30, 2003.

The therapeutic biological products include:

- Monoclonal antibodies for in-vivo use
- Cytokines, growth factors, enzymes, immunomodulators; and thrombolytics
- Proteins intended for therapeutic use that are extracted from animals or microorganisms, including recombinant versions of these products (except clotting factors)
- Other non-vaccine therapeutic immunotherapies
- All Biologics are required to file BPDR for any product deviations per 21CFR 600.14, and these will be reviewed by either CBER or CDER per the assigned jurisdiction

Biologics Definition



- Re-defined Biologic product by BPCI (2009) and transitioned on March 23, 2020.
- Biologics Definition:

The BPCI Act clarified the statutory authority under which these protein products will be regulated by amending the statutory definition of a "biological product" in the PHS Act to include a "protein (except any chemically synthesized polypeptide)," and describing procedures for submission of a marketing application for these protein products. The Further Consolidated Appropriations Act, 2020, enacted on December 20, 2019, further amended the definition of a "biological product" in the PHS Act to remove the parenthetical "(except any chemically synthesized polypeptide)" from the statutory category of "protein," meaning that such chemically synthesized products are now within the definition of "biological product" and subject to the statutory transition. This legislative change only affects chemically synthesized products that fall within the interpretation of "protein" (see updated Preliminary List below); this legislative change does not affect "peptides" (i.e., polymers composed of 40 or fewer amino acids).

Biological Product Deviation Reports (BPDRs)

- FDA
- FDA has developed FORM FDA 3486, a standardized reporting format that may be submitted in paper form by mail. FORM FDA 3486 is used to report biological product deviations.
 - https://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM061463.pdf
- CBER Submission: Electronic Submission of Biological Product Deviation Reports (eBPDR)
 - BPDRs can be submitted electronically via the Internet (for CBER submission only)
 - A valid Registration or CLIA (Clinical Laboratory Improvement Amendment) Number is required to use this eBPDR system at CBER. If firm does not have a valid Registration Number, they should contact the local FDA district office to obtain a Registration Number from the appropriate Registration Monitor (Blood, Device, or Drug).
- CDER Submission: separate from eBPDR system and via e-mail or paper submissions

FORM FDA 3486

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BPD Code Categories for Non-Blood Products

The BPD Code is made up of three levels.

The first level (XX) identifies the system affected in which there was a breakdown or failure, which resulted in the distribution of an unsuitable product. Use the appropriate guidance document for determining the system affected.
BPD Code | XX | - | | - | | - |

Summary of Product Codes by Type of Product

For blood products the systems include:	For non-blood products the systems include:	For HCT/Ps the systems include:
DS - Donor Screening	IM - Incoming Material Specifications	DE - Donor Eligibility
DD - Dooor Defemal	PC - Process Controls	DS - Donor Screening
BC - Blood Collection	TE - Testing	DT - Donor Testing
CP - Component Preparation	LA - Labeling	FA - Facilities
VT - Transfusion-Transmitted Infection Testing	PS - Product Specifications	EC - Environmental Controls and Monitoring
RT - Routine Testing	QC - Quality Control and Distribution	EQ - Equipment
LA - Labeling		SR - Supplies and Reagents
QC - Quality Control and Distribution		RE - Recovery
		PC - Processing and Process Controls
		LC - Labeling Controls
		ST-Storag e
		SD - Receipt, Pre-Distribution, Shipment and Distribution



6-Character BPD Code Example

PS-53-** Stability testing failed PS-53-01 Other PS-53-02 Potency PS-53-03 Preservative PS-53-04 Container closure integrity PS-53-05 Chemical analysis/purity PS-53-06 Moisture PS-53-07 pH PS-53-08 Appearance

†PS-54-** Administration set, or device constituent part (packaged with product) did not meet specifications PS-54-01 Other PS-54-02 Incorrect or missing label PS-54-04 Expired

QC-**-** QUALITY CONTROL AND DISTRIBUTION

QC-60-** Miscellaneous QC-60-01 Other

QC-61-** Product distributed inappropriately

QC-61-01 Other QC-61-02 Product distributed prior to completion of required testing QC-61-03 Product distributed prior to CBER approval of a PAS

QC-61-04 Product distributed less than 30 days after submission of CBE-30 or prior to submission of CBE-30

QC-61-05 Product distributed prior to validation of process

QC-61-06 Outdated product distributed

QC-61-07 Product distributed prior to record review or release by the quality control unit

QC-62-** Shipping and storage

QC-62-01 Other

QC-62-02 Product shipped at incorrect temperature

QC-62-03 Product stored at incorrect temperature

QC-62-04 No documentation product was shipped or stored at appropriate temperature

QC-63-** Product identified as unacceptable, and not quarantined QC-63-01 Other

QC-64-** Packing

QC-64-01 Other QC-64-02 Vial missing QC-64-03 Packaged incorrectly †QC-64-04 Broken or cracked vial/syringe/container/device constituent part QC-64-05 Improper orientation (e.g., sideways)

FORM FDA 3486 (Cont.)

Biological Product Deviation Report



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FORM FDA 3486 (Cont.)

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Biological Product Deviation Report

Biological Product Deviation Report

Biological Product Deviation Report

FDA

Most Common Reporting Errors from FORM FDA 3486 in CDER BPDR Program



- Listing multiple applications and/or products under one form
- Reporting to the incorrect center or office
- Having the reporting firm information that does not match our data
- Having the wrong/inappropriate problem firm
- Inappropriate defect code
- Did not refer to general instructions while preparing for the report submission
- Refer to CDER BPDR website for submission recommendation to CDER BPDR program

https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/ cder-biological-product-deviations



CDER BPDR Submission Recommendations



- One BPDR must be submitted per Biological License Application (BLA) product impacted by the deviation;
- Wherever possible list BLA application information during reporting;
- Multiple lots of the same BLA product impacted by the same deviation be reported in one BPDR;
- Multiple complaints with similar root cause for one BLA product be reported in one BPDR provided that these complaints were received within 45 calendar days from the date of discovery;
- Wherever possible, indicate in the initial report whether additional follow-up or final reports are expected.
- Electronic submission to CDER DQRS Reports mailbox is preferred: <u>CDERDQRSREPORTS@fda.hhs.gov</u>;
- Custom reports attached to FDA FORM 3486 or any submissions without FDA FORM 3486 is discouraged.

How to Avoid Information Request(s) After BPDR Submission



- Provide as much information of the description of the deviation that includes defect and scope assessment.
- Provide Root Cause Analysis for clear and logical investigation. Include details for appropriate actions to prevent recurrence.
- Provide any Corrective Action and Preventative Action (CAPA) plans that are designed based on the root cause identified.
- Provide BLA and relevant product information.
- Select the best representation of the defect code from the current BPD code list.
- Provide information accurately per the general instructions for BPDR submission.
- Provide relevant data in the report to allow appropriate assessment and/or product quality evaluation.
- Provide information to all fields in the FORM FDA 3486.
- Avoid custom reports attached to the end of the form.
- Adhere to the commitments stated in the initial report. www.fda.gov

Summary



- When a product quality deviation occurs, the manufacturer and applicant holder should initiate a retrospective root cause analysis of the failure mode. It should be implemented based on a pre-defined protocol that includes affected lots and a sampling strategy for testing.
- This plan should outline critical control points of the manufacturing process and demonstrate performance of the drug or biological product.
- When conducting a root cause analysis of a product or performance issue, the traceback of the causality should begin at the lowest level where the failure occurred.

Summary



- When a deviation occurs, three working days are required for the submission of a FAR by the A/NDA applicant holders; and 45 days for a BPDR by the BLA applicant holder for biologics.
- The use of FDA forms 3331a for FARs and 3486 for biologicals are encouraged.
- These reports should include complete and accurate assessment of the detailed root cause investigations and Corrective Action and Preventative Action (CAPA) Plans.

Challenge question #1



Q: Is there always a causal relationship between product quality deviations and adverse events?

Answer to Challenge Question #1





Challenge Question #2

Q: What is the value of having a standardized format for reporting drug product quality reports?



Answer to Challenge Question #2

References for FAR



- 3331a FDA form and instructions: <u>https://www.fda.gov/about-fda/reports-manuals-forms/forms</u>
- Field Alert Report Guidance: <u>https://www.fda.gov/drugs/surveillance/field-alert-reports</u>
- Field Alert Report From: Questions and Answers <u>https://www.fda.gov/drugs/surveillance/field-alert-report-form-questions-and-answers</u>
- Field Alert Report Submission Questions and Answers- Guidance for Industry July 2021
- <u>https://www.fda.gov/regulatory-information/search-fda-guidance-documents/field-alert-report-submission-questions-and-answers-guidance-industry</u>

References for BPDR

CDER BPDR website:



https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/cder-biological-product-deviations

FDA Guidance for Industry on Biological Product Deviation Reporting for Licensed Manufacturers of Biological Products Other than Blood and Blood Components:

http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/General/UCM16392 3.pdf.

FORM FDA 3486:

https://www.fda.gov/media/70604/download

Deviation Codes:

https://www.fda.gov/vaccines-blood-biologics/report-problem-center-biologics-evaluation-research/biological-product-deviation-reporting-and-hctp-deviation-reporting-deviation-codes

Non-Blood Product Codes:

<u>https://www.fda.gov/vaccines-blood-biologics/report-problem-center-biologics-evaluation-research/biological-product-deviation-reporting-and-hctp-deviation-reporting-non-blood-product-codes</u>

Postmarketing Safety Reporting for Combination Products Guidance for Industry and FDA Staff:

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/postmarketing-safety-reporting-combination-products

www.fda.gov

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Thank you!

